

Factors Associated with Age of Onset of Bipolar Affective Disorder from a Tertiary Care Hospital in Southern India: A Cross-sectional Study

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ABSTRACT

Introduction: Bipolar Affective Disorder (BPAD), is a chronic debilitating disorder. The mean age at onset for BPAD is observed to be around 20-30 years. The Age at Onset (AO) of BPAD is affected by various factors, including gender, family history, substance use, and other environmental factors.

Aim: To assess the AO of BPAD in the clinical population and the relationship of socio-demographic and clinical factors with AO.

Materials and Methods: A cross-sectional study, was conducted at Department of Psychiatry, Chettinad Hospital and Research Institute, Kelambakkam, Tamil Nadu, India, from January 2020 to January 2021. The socio-demographic details of total of 53 participants suffering from BPAD attending the tertiary care psychiatric setting were collected. The AO of the sample data and its correlation with gender, family history, substance use, marital status, residential background, etc. was analysed by using Statistical Package for the Social Sciences (SPSS) version 22.0. Independent t-test and one-way Analysis of Variance (ANOVA) were applied to compare AO among different variables. Pearson's correlation coefficient and multiple linear regression were applied to assess the correlation.

Results: Out of the 53 participants, 30 participants (56.6%) were males and 23 (43.4%) were females of which 31 (58.5%) of the participants had a family history of psychiatric illness. Eighteen (33.8%) had some substance use before onset. No substance use was reported by females. The mean AO of the sample was 24 ± 7.8 years. The mean AO was significantly earlier for, males ($t = -2.598$; $p = 0.012$), those with a family history of psychiatric illness ($t = -2.968$; $p < 0.01$) and urban dwellers ($t = -3.752$; $p < 0.01$). Multiple linear regression analysis showed only family history ($B = -3.07$, $p = 0.01$) and urban background ($B = 3.60$, $p = 0.01$) significantly predicted earlier AO. AO also negatively correlated with number of suicides per person years of illness ($r = -0.387$; $p < 0.01$), and number of episodes per person years of illness ($r = -0.322$, $p = 0.01$).

Conclusion: Presence of a family history of psychiatric illness and residing in urban areas showed an overall early prediction of AO rather than gender, and other environmental factors. Earlier AO was associated with worse clinical outcomes of BPAD. Knowledge about AO and its factors might help in predicting treatment outcomes, and in planning primary preventive strategies for vulnerable populations.

Keywords: Biopsychosocial, Mood disorders, Psychiatric illness, Risk factors

INTRODUCTION

The BPAD is a chronic debilitating disorder involving episodes of severe mood disturbance and personality changes, neuropsychological deficits, physiological changes, and disturbances in functioning. In addition, manic episode puts the individual at a risk of violence, getting into criminal records, reckless spending and debts, while the depressive episodes bring a risk of decreased productivity, interpersonal distress and missed opportunities [1]. According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) the lifetime prevalence of BPAD is 2.6% [2]. Indian studies estimate a lifetime prevalence of around 2.4-3.0% for BPAD [3]. The heterogeneous clinical presentations, varied response to treatment and presence of co-morbid illnesses like substance use, anxiety disorders, self-harm and suicidality, and a lack of adequate preventive strategies make the illness difficult to treat and poses a challenge to the mental healthcare providers worldwide. The India State-Level Disease Burden Initiative reports the Disability-adjusted Life-Years (DALYs) contributed by BPAD was around 6.9% of all mental disorders [4].

Epidemiological studies usually consider the AO of illness as the age at which the disease is first clinically identified. Global epidemiological studies have established BPAD as an early onset illness with mean AO varying around 20-30 years [1]. A study done from the data from

first 1000 participants of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study compared clinical course, co-morbidity and quality of life of three different groups based on their AO of BPAD, and found earlier AO correlated to more severe symptoms, longer duration and more co-morbidities [5]. Subsequently studies on juvenile and early onset BPAD speculate a possibility of them being a subset of BPAD [6]. Further research is being done to establish early onset BPAD as a distinct phenotype with its own features and course. Even though earlier onset has shown poorer outcomes, early intervention studies are providing promising results in reducing the morbidity of the disease [7].

Aetiology of BPAD is multifactorial, with complex inter-relationship. Broadly they could be studied as genetic risk factors and environmental risk factors. These risk factors are assumed to affect the AO of BPAD. Genetic factors like history of mood disorders or substance use disorders in the family have shown to be associated with earlier AO, while factors like gender have shown varied results, with earlier studies showing females having earlier AO and more recent studies showing males having earlier AO [8,9]. Environmental factors have also shown varying associations with the AO. Substance use like alcohol, cannabis and opium have been strongly associated with early AO [10]. Other socio-demographic factors like marital status, background, type of family are also associated with earlier AO of BPAD [11].

Most of the literature are the studies from the western world. In the developing nations, especially India, epidemiological studies of BPAD and factors affecting AO are not adequate [12]. Culture significantly effects the environmental risk factors of BPAD like behaviour, coping and functioning of people. In a country facing severe stigma to mental health and shortage of mental health resources, any knowledge about factors effecting the AO of BPAD would help in formulating primary prevention, better treatment plans and providing direction for future research. The present study was done with an objective to assess the AO of BPAD in an Indian clinical setting and, to assess the relationship of AO with various socio-demographic and clinical factors.

MATERIALS AND METHODS

A cross-sectional study was conducted at the tertiary care setting of the Department of Psychiatry, Chettinad Medical College and Research Institute, Kelambakkam, Tamil Nadu, India. The data of participants attending the Psychiatry tertiary care setting was collected over a period of one year, from January 2020 to January 2021. The study received ethical clearance (585/IHEC/11-19 dated 5/12/2019) from the Institutional Human Ethics Committee. On a convenient sampling basis, 53 participants were included in the study.

Inclusion criteria: It included all patients aged 18-60 years, who were willing to give written informed consent, and fulfilling the International Classification of Diseases 10th Revision (ICD-10) criteria for BAPD (F.31) [13].

Exclusion criteria: Those patients with inadequate or unreliable history regarding the study details were excluded from the study.

Study Procedure

After managing for any acute symptoms and obtaining written informed consent from the patient, a detailed case work-up was done. A semi-structured proforma was used for collecting socio-demographic details. It comprised of details of age and gender. Education was grouped under illiterate, primary school, secondary school, high school 12th standard, graduation and post-graduation education. Employment status was grouped under unemployed, part time jobs including unskilled work, and fulltime jobs including semi-skilled, skilled/clerical, professional work. Type of family included either nuclear or joint families. Marital status included married/living with a partner or single/divorced. The socio-economic status was grouped as lower, upper lower, lower middle, upper middle and upper class based on modified kuppaswamy method [14]. Residential background was grouped under either rural or urban. Detailed history of the illness including the age at onset of illness, course of illness, number of mood episodes, number of hospitalisations, presence and type of substance use at onset, suicide attempts was collected. In order to better understand and analyse the severity of illness, the data regarding number of mood episodes, number of hospitalisations and suicide attempts were averaged according to the person years of illness (duration from onset of illness to the time of assessment). This data was presented as average number of episodes/hospitalisation/suicide attempts per person years of illness respectively. For the purpose of statistical analyses, variables for education were converted into <12th and ≥12th standard; Employment into no/part time and full time employment. Socio-economic status was converted into lower (comprising of lower, upper lower and, lower middle classes) and upper (comprising of upper middle and, upper classes).

All 53 participants were able to complete the interview. The age at which, the symptoms necessary for the diagnosis of mania, hypomania or depression first appeared, was considered as AO, rather than the age at which first hospital contact was made. This history was further consolidated on interviewing the family members and going through older records, if available, in an attempt to get an accurate estimate of the AO. The reliability of history was assessed by the investigators based on the corroboration of history with the attender and or available records, the relation, duration of interaction with the patient and the observational ability of the attender.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 22.0. Descriptive statistics were used to analyse the characteristics of the study population. The severity of illness of the subjects i.e., suicide attempts, number of illness episodes, and number of hospitalisation due to the illness were standardised by averaging them per person years of illness. The independent t-test was used to find the differences in mean AO of the variables. One-way ANOVA was used to compare AO for different types of substance abuse. Pearson's coefficient correlation was done to assess the correlation of AO with socio-demographic, clinical, and severity of illness variables. Multiple linear regression analysis was conducted to determine whether the variables with bivariate analysis could predict AO. For all statistical test p-value significance tests, set at <0.05.

RESULTS

A total of 53 participants were analysed. Mean age of the population was 31±10 years. Among the participants, 30 (56.6%) were males and 23 (43.4%) were females. The sample had 26 urban residents (49.1%) and 27 rural (50.9%) residents. Thirty one patients (58.5%) had an education of 12th standard or above. Only 14 (26.4%) of them were holding a full time job while the rest had only part-time or no jobs at all. Twenty five patients (47.2%) were married, while the rest 28 (52.8%) were unmarried/separated.

The mean AO was 24±7.8 years. The mean duration of illness of the population was 6.6± 6.3 years. Of the patients 31 (58.5%) had a family history of psychiatric illness. Eighteen (34%) patients had some sort of substance use, and no female patient had reported use of substance. Of all the abusers, 8 (44.4%) had alcohol use, 5 (27.8%) had cannabis use, and 5 (27.8%) patients had mixed pattern of drug use. No opioid use was reported among the patients. The mean average of suicide attempts per person years of illness was 0.12±0.21, the mean average number of episodes per person years of illness were 0.80±0.40, and the mean average number of hospitalisations per person years of illness were 0.43±0.28.

The mean AO was significantly earlier ($t=-2.598$; $p=0.012$) for males than females, unmarried/separated subjects than married subjects ($t=-4.729$; $p<0.01$), urban dwellers than rural dwellers ($t=-3.752$; $p<0.01$). Subjects with a family history of psychiatric illness had significantly earlier AO ($t=-2.968$; $p<0.1$) than those with no history. The presence of substance use had no significant differences in mean AO, but when compared only in male subjects, AO was significantly earlier in group with substance use ($p=0.021$). There was no significant variation in the mean AO among the different subgroups of substance user. The comparison of the mean AO in different socio-demographic variables is given in [Table/Fig-1].

Socio-demographic variables		Age at onset	T (Independent t-test)/F (One-way ANOVA)	p-value
		Mean±SD		
Sex	Male	22.60±4.03	-2.598	0.012*
	Female	27.78±9.93		
Education	≤12 th Standard	26.58±9.8	1.092	0.054
	>12 th Standard	23±4.8		
Employment	No/Part-time	25±8.48	0.871	0.388
	Full-time	23±2.51		
Socio-economic status	Lower	25.5±8.25	0.757	0.453
	Upper	24±6.61		
Marital status	Unmarried/ Separated	21±3.40	-4.729	<0.01*
	Married	29±8.57		
Type of family	Nuclear	24±6.90	-1.55	0.125
	Joint	27±8.81		
Background	Urban	21.3±3.56	-3.752	<0.01*
	Rural	28.26±8.84		

Family history of psychiatric illness	Absent	28±8.23	-2.968	<0.01*
	Present	22.4±6.13		
Substance use	Absent	24.49±8.85	-0.85	0.399†
	Present	23.6±4.10		
Type of substance use	Alcohol	25±4.75	0.966	0.403
	Cannabis	22±3.81		
	Mixed Use	23±3.03		

[Table/Fig-1]: Comparison of age at onset among socio-demographic variables. SD: Standard deviation; *signifesp value <0.05 is taken significant; †When AO and substance use were compared only in men, AO was earlier in males with substance use (p=0.021). (Statistical test used: independent t-test, one-way ANOVA.)

Pearson's biserial correlation showed a significant positive association of AO for females ($r=0.34$, $p=0.43$), urban residential background ($r=0.46$, $p=0.01$) and married subjects ($r=0.40$, $p=0.12$). A significant negative correlation was found between AO and the presence of family history of psychiatric illness ($r=-0.38$; $p<0.01$). The multiple linear regression analysis was conducted, using socio-demographic and clinical variables. Multicollinearity was checked using tolerance statistic and variance inflation factor, which did not reveal significant multicollinearity. The model was statistically significant ($F=3.7$; $p=0.02$) and explained 43.9% of the variance in AO. It was observed that a family history of psychiatric illness ($B=-3.07$, $p=0.01$) and urban background ($B=3.60$, $p=0.01$) suggested a trend of earlier AO, as given in [Table/Fig-2]. The correlates and predictors for AO of BPAD is given in [Table/Fig-2].

Variable	r	Beta	95% CI	t	p
Females	0.34 ^a	0.14	-3.35-7.66	0.79	0.43
>12 th standard education	-0.22	0.03	-3.02-3.84	0.23	0.81
Urban residency	0.46 ^b	0.36	1.19-9.82	2.57	0.01*
Full time job	-0.11	-0.15	-7.39-2.13	-1.11	0.27
Joint Family	0.21	0.08	-2.90-5.59	0.64	0.52
Married	0.40 ^b	0.21	-0.72-5.81	1.56	0.12
Upper-class socio-economic status	-0.10	0.08	-2.60-5.31	0.690	0.49
Family history of psychiatric illness present	-0.38 ^b	-0.30	-8.28-1.07	-2.61	0.01*
No substance use	0.11	-0.01	-5.67 to 5.16	-0.094	0.92

[Table/Fig-2]: Socio-demographic and clinical correlates age at onset of bipolar affective disorder. r =Pearson's correlation coefficient, ^a=one tailed significance $p<0.05$, ^b=two tailed significance $p<0.01$, Beta=Standardised Correlation coefficient of multiple regression, CI=Confidence interval. * p -value <0.05 is significant. (Statistical tests used: Pearson's Correlation test, Multiple linear regression analysis)

A significant negative correlation was found between AO and the average number of suicides attempts per person years of illness ($r=-0.387$; $p<0.01$), and average number of episodes per person years of illness ($r=-0.322$; $p=0.01$) as given in [Table/Fig-3]. The association of AO with various severity of illness variables is given in [Table/Fig-3].

Illness variables	r-value (Pearson's correlation coefficient)	p-value
Average mood episodes per person years of illness	-0.322	0.01*
Average hospitalisations per person years of illness	-0.214	0.12
Average Suicide attempts per person years of illness	-0.387	<0.01*
Presence of substance use	-0.11	0.39

[Table/Fig-3]: Association of age at onset with course and severity of illness variables. *Signifesp value <0.05 is taken significant. (Statistical tests used: Pearson's Correlation test)

DISCUSSION

Bipolar Affective Disorder is a chronic illness with multifactorial risk factors. Many epidemiological studies have shown that the risk factors associated with the pathophysiology of BPAD would lead

to an earlier onset of illness. The study was set out to investigate various factors affecting AO in a tertiary care setting. The mean AO of BPAD in the subjects were similar to the mean AO reported in the World Mental Health Survey Initiative done by World Health Organisation (WHO) across various nations across the globe [1]. The male subjects had significantly earlier onset of BPAD when compared to females. This finding was consistent with the 35-year incidence study on gender differences in BPAD by Kennedy N et al., [9]. A hypothesis of neuroprotective action of oestrogen against the abnormal neural developments in psychotic disorders is being proposed in recent studies [15,16].

Leboyer M et al., concluded from their review that genetic factors and familial transmission have a bigger role in the early onset 'subgroup' of BPAD [17]. The present study similarly shows the subjects with a history of psychiatric illness have earlier AO's than those without a family history. The gender of the subject seemed to have no correlation with the family history, further establishing this finding.

Multiple studies have shown that the odds of developing BPAD increased with early use of substance use like cannabis, alcohol, cocaine and opioids [10,11,18]. However, the present study shows no significant difference in AO for subjects with substance use during onset, this could be attributed to the fact that no female subject (43.4% of study sample) had reported substance use, and when compared only in men; men with substance use had earlier onset. A recent systematic review on co-morbid substance use in BPAD had similarly reported that substance use was more prevalent in men than women with BPAD, and men with co-morbid substance use had earlier onset [19]. The studies regarding the dosage of drug use that could trigger first episode of BPAD are inconclusive, and the difference between different substance had not been studied [10,17]. The present study had no reports of opioid use. Among the three subgroups of substance use alcohol, cannabis, and mixed pattern, there was no significant difference in the AO. Cultural conservative attitudes towards substance could have also led to later AO in females. However, on multiple regression analysis this correlation did not persist. A genetic predisposition to psychiatric illness seems to have a strong predictive value on the early onset of BPAD in spite of other biological and socio-cultural protective factors of females in India.

Unmarried and separated subjects had significantly younger AO than those who were married. Studies on role of life partners in the onset and course of BPAD have shown favourable outcomes for married groups but the correlation did not persist after doing multiple regression analysis. Urban dwellers had earlier onset of illness than rural dwellers, and urban residential background moderately predicted earlier AO of BPAD [20]. A cohort study by Kaymaz N et al., have found greater incidence of BPAD in urban areas and conclude that early environmental interaction with stressful urban environment like social isolation and cohesion could lead to earlier onset and greater incidence [21].

Subjects with earlier onset of illness also had a greater number of suicidal attempts, and had a greater number of mood episodes in their illness period. This inverse relationship between the AO and severity of illness factors like average number of suicides, number of episodes per person years of illness, are similar to severity of illness studies in the past [6,22]. These findings provide further proof for the significant DALYs contributed by BPAD. The presence of strong genetic association, gender difference and increased severity of illness also give further evidence for considering a separate early onset phenotype of BPAD.

Limitation(s)

The findings of the study are limited by the cross-sectional nature of the study, short duration, and the risk of selection bias and recall

bias. A small sample size prevents the generalisability of the study findings. There is a need for similar but, larger multicentric prospective studies to provide more evidence on risk factors predicting earlier onset of illness, while also considering socio-cultural factors of the developing world. As it is understood that patients with early AO have more severity of the illness, the factors associated with AO require more emphasis while taking history. The presence of a family history could help to identify at risk groups in the siblings and children of the patient and help in screening and early interventions. Studies have been showing positive outcomes with early interventions in at-risk groups in the western world [7]. Similar studies are needed in the developing countries, where there is a greater need to bring down patient morbidity and demand on the mental health services with an effective early intervention strategy.

CONCLUSION(S)

Male gender, a family history of psychiatric illness, substance use and urban background indicated an earlier onset of BPAD. Even though cultural differences in substance use in addition to the hypothesised protective role of oestrogen could delay the onset of illness in women, family history and environmental factors like urban background could be better predictors of early AO of BPAD. The subjects with early AO are more vulnerable to suicide attempts, and a greater number of mood episodes in their illness period, increasing the morbidity. There is a need of prospective studies, that identify the specific indicators of early onset BPAD in the developing countries, in order to help formulate early interventions plans that tackle the increasing mental health burden of BPAD.

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