ORIGINAL RESEARCH PAPER

Psychiatry

PREVALENCE OF RISK FOR OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH BIPOLAR DISORDER

KEY WORDS: Bipolar disorders, Obstructive sleep apnea, sleep

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ABSTRACT

Background: An association exists between obstructive sleep apnea (OSA) and Bipolar disorder (BD). The prevalence of OSA in BD has significantly increased during the past 2 decades. We aimed to assess the prevalence of risk for OSA in BD. **Methods:** This was a hospital based, cross-sectional, case control study. Out of 218 participants enrolled in the study, 109 had BD and 109 were recruited for the comparison in the control group. All the participants were asked to complete the Berlin Questionnaire, a self assessment tool to establish the risk for OSA. **Results:** about two-third of the patients with BD were found to be at risk for OSA as compared to the 19.27% prevalence in the control group. Patients of BD in high risk for OSA were males, had significantly higher BMI, with co morbid physical illnesses and in those who were on combination of valproate and lithium in comparison to valproate alone. **Conclusion:** Patients with BD had significantly higher BMI in comparison to controls. In comparison to controls, significant higher percentage of patients with BD had higher risk for OSA in comparison to healthy controls. Our finding of over half of patients being in the high risk range should be sufficient to sensitize clinicians and raise awareness concerning OSA in BD.

INTRODUCTION

In comparison to general population, patients with Bipolar disorder (BD) are at an increased risk of medical co morbidities like diabetes mellitus(DM), cardiovascular diseases(CVD), metabolic syndrome(Mets), and obstructive sleep apnea (OSA).[1][2][3][4][5]

Sleep disturbances are the core symptoms of BD [6] [7] with a great variability in sleep duration.[8]

In patients of BD the decreased need for sleep predicts the onset of a manic or hypomanic episode, the following day [9], whereas sleep extension occurs frequently in the depressive episodes.[10][11][12]

The frequent disturbance in sleep-wake cycle tends to exacerbate or precipitate frequent mood episodes [13], and thereby acts as a risk factor for relapse of a mood episode.[14] It has been seen that sleep deprivation can trigger manic episodes in animal BD models too. [15][16] Lack of sleep in patients with BD is a symptom for poor prognosis, and also increasing the risk of suicide in patients with past suicidal attempt. [17] Sleep disturbances are quite common in patients with BD even during symptom free period of illness.[7]

From the above findings and depending on the rhythmic nature of BD, it can be said that endogenous circadian system plays an important role in clinical presentation, etiology and outcome in BD.[18][19]

Part of the detrimental effect of these conditions on mood regulation may be ascribed to underlying sleep-related breathing problems. Patients who develop OSA as a result of cumulative risk factors may be over-represented among those who present a history of chronic and treatment-resistant depressive symptoms.

Since the depressive phase of BD is often chronic and difficult to treat, and undiagnosed underlying medical conditions may greatly contribute to its unfavorable outcome, it is reasonable to speculate that sleep-disordered breathing may play a role in this clinical picture. Indeed, the presence of medical co-morbidities that constitute risk factors for OSA has been associated with a worse outcome of BD. [20] For example; obesity has been linked to a higher number of lifetime depressive episodes and to a shorter time to relapse. [21] Abdominal obesity, particularly, is associated with increased suicidality.[3]

Therefore, this study was taken to examine whether BD was associated with an increased risk of subsequent OSA using the sex- and age-matched healthy voluntary controls.

MATERIALS AND METHODS:

Study design

This cross-sectional, case control study was conducted at institute of mental health and neurosciences Kashmir which is an associated hospital of Govt. Medical college,Srinagar. The patients with BD currently in euthymic phase of illness were recruited for the study. Euthymia for this study was defined as Hamilton depression rating scale (HDRS)[22] and Young mania rating scale (YMRS)[23] score of ≤7.This study was conducted over a period of eighteen months from mid June 2020 to mid December 2021 after seeking permission from institutional ethics committee. The patients were selected through purposive sampling technique after informed written consent.

Inclusion criteria that were adopted included (1) age of ≥18 years; (2) euthymia for at least 3 months prior to participation in the study ; (3) Those who gave written informed consent.

Patients receiving treatments for any medical illness known to alter sleep patterns, substance use disorder, being hospitalized, being involved in shift work, those with recent history of trans-meridian travel or a history of major life event were excluded from the study.

Age and gender matched voluntary healthy controls where recruited through adverts who gave written informed consent.

Demographic and clinical variables:

Basic demographic data, clinical details and treatment records were collected from the patients/relatives and medical records section. Height, weight and neck circumferences were measured in all the patients. The YMRS and HDRS scales were used for quantifying the severity of current manic or depressive symptoms.

Berlin sleep questionnaire [24] is a 10-item valid instrument which is used globally to determine the risk of OSA. In this instrument category 1 risk is defined as persistent symptoms reported in response to two or more questions about snoring. Category 2 assess persistent occurrences of drowsy driving, wake time sleepiness or both. Category 3 risk factors include factors like high body mass index (BMI 30/m^2 and high blood pressure (140/90) or the use of antihypertensive medication. Individuals are classified as high risk for OSA if they meet high risk criteria in two of the three categories. Positive predictive value of the instrument was found to be 0.88.[25]

The Epworth sleepiness scale [26] is an 8-item questionnaire which is widely used as a subjective measure of patient's day time sleepiness. The test is a list of 8 situations in which patients rate the tendency to become sleepy on a 4-point scale ranging from 0, no chance of dozing, to 3, high chance of dozing (0-3) and the scores range from 0-24. A total score of 10 indicates clinically significant day time sleepiness.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences, twenty-third versions (SPSS-23) [27]. The data were analyzed in the form of frequencies, percentage, mean, and standard deviation. Comparisons were done using the Chi-square test and *t*-test.

RESULTS:

A total of 218 participants were enrolled in the study, out of which 109 had BD and 109 were for comparison in the control group. Patients and controls were matched for age, gender, family type and occupation. As can be seen in the table 01, significantly higher proportions of those in the control group were educated beyond matric. Participants with BD had a mean age of onset of 32.90±5.17 years, with the mean duration of illness of 18.78±5.17 years, and the mean number of life time mood episodes was 8.78±4.17. The mean YMRS scores was 2.266±1.05 and the mean HDRS score was 1.87±0 .61.

Mean years of schooling was 8.78±3.90 years in cases in comparison to controls (**10.10±3.83)**. The mean height, weight and waist circumference were significantly higher in cases than controls. In terms of anthropometric measures, compared to the healthy controls, patients with BD had significantly higher BMI, as shown in table 2.

In comparison to controls, higher percentage of patients with bipolar disorder had higher risk for OSA in comparison to controls and the difference was statistically significant, as shown in table 02.

On comparing patients of bipolar disorder and normal healthy controls, a significantly higher proportion of cases where having higher BMI, significantly higher proportion of them had BMI of ≥25, and had significantly higher prevalence of patients with co morbid physical illnesses as shown in table 03.

Significantly higher risk for sleep apnea was seen in those who were on combination of valproate and lithium in comparison to valproate alone. When the patients of BD, at low and high risk of OSA were compared, it was seen that patients at high risk were significantly more often males, and having comorbid physical illnesses.

Table 01: Demographic characteristics of study groups

Parameter	Cases	Controls	χ2/t-test/Mann-whitney
Age	32.90±5.17	32.56±5.30	T=0.4786
Gender Male Female	 78(71.56) 31(28.44)	 78(71.56) 31(28.44)	χ2=0.0001(1)
Education <matric ≥ matric	 45(41.28) 64(58.72)	 23(21.10) 86(78.90)	χ2=10.34 (0.001)
Occupation Unemployed Employed	 70(64.22) 39(35.78)	 67(61.47) 42(38.53)	χ2=0.17(0.674)
Family type Nuclear Non-nuclear	 84(77.06) 25(22.94)	 88(80.73) 21(19.27)	χ2=0.44(0.507)
Locality Urban Rural	 93(85.32) 16(14.68)	 79(72.48) 30(27.52)	χ2=5.40(0.020)

Table: 02, Anthropometric variables of study groups

Parameter	Cases	Controls	χ2/t-test/Mann-whitney
Mean years of schooling (SD)	8.78±3.90	10.10±3.83	t = 2.50
Height(CM), mean(SD)	170.66±5.12	168.89±4.66	t=2.66(0.0041)
Weight(KG),mean(SD)	82.57±16.94	74.08±10.76	t=4.41(0.0001)
WC (cm), mean (SD)	93.55±14.36	83.00±12.16	t=5.84(0.0001)
BMI (kg/m2), mean (SD)	28.23±4.99	25.94±3.38	t= 3.97(0.0001)

Table: 03, clinical characteristic of study groups

Parameter	Cases	Controls	χ2/t-test/Mann-whitney
BMI (kg/m2), n (%) ≥25 <25	 74(67.89) 35(32.11)	 52(47.71) 57(52.29)	χ2= 9.10(0.003)
Smoking No Yes	 35(32.11) 74(67.89)	 82(75.23) 27(24.77)	χ2=40.75(0.001)
Co-morbid physical illness No Yes	 88(80.73) 21(19.27)	 91(83.49) 18(16.51)	χ2=0.28(0.596)
Clinically Significant Daytime Sleepiness No (ESS≤10) Yes(ESS>10)	 56(51.38) 53(48.62)	 101(92.66) 56(51.38)	χ2= 46.09(0.001)
At risk for OSA No Yes	 34(31.19)/ 75(68.81)	 88(80.73) 21(19.27)	χ2=54.28(0.001)

DISCUSSION:

OSA is a common chronic breathing disorder affecting 2–4% of the adult population that involves recurrent collapse of the upper airways leading to episodes of hypoxemia and arousal during sleep.[28][29]

Daytime sleepiness, due to nocturnal sleep fragmentation, is a key symptom of OSA, being present in more than 80% of the patients. As the disorder progresses, the sleepiness becomes increasingly dangerous, causing impaired performance at work and major work-related and road traffic accidents.[30][31]

In the present study, about two-third of the patients with BD were found to be at risk for OSA, and this was significantly higher than that observed in the matched healthy control

group. At least three possible explanations may be worth considering in regards to the link between BD and the risk of OSA. Firstly, different types of sleep disturbances described in all phases of BD, including remission. [32] Second, sympathetic hyperactivity and hyper-arousal associated with sleep disturbances may lead to instability of the upper respiratory tract, and may contribute to subsequent OSA. [33] Third, benzodiazepines prescribed for sleep problems lead to muscle relaxation and in turn lead to the collapse of the airways.[34]

Our results resonate with other authors who reported the prevalence of OSA to vary from 22% to 54.1% in clinical settings. [35][36][37] The studies where authors have used Polysomnography, have reported the prevalence of OSA to be 22%.[37][38]

In the present study, cases of BD had significantly higher BMI in comparison to the healthy controls. Some of the previous studies, have also reported the mean BMI of the sample to range from 29.18 to 36.80 kg/m^2, [35] [36] [37] and thus coincides with our study results.

BMI is one of the important predictor of OSA.[39] Many patients with OSA can develop cognitive and neurobehavioral dysfunction, inability to concentrate, memory impairment and mood changes such as irritability and depression which further impairs performance at work with a remarkable effect on the quality of life.[40]

It is a well established fact that OSA, if left untreated, is a major determinant of cardiovascular morbidity and mortality. [41][42] The main cardiovascular disorders described include drug-resistant systemic hypertension (>50% of the patients), ischemic heart disease, cardiac arrhythmias and stroke.[41]

Recently, sleep-related hypoxia has also been associated with a low-grade systemic inflammation, which in turn may contribute to initiate or accelerate the process of atherogenesis.[31] Therefore, OSA is often associated with the symptoms of metabolic syndrome.[43]

Patients with BD have an unhealthy lifestyle exacerbated by mood symptoms and poorer access and quality of physical health care, which increases the likelihood of developing a metabolic syndrome.[44][45] In addition, an important metabolic impairment occurs in OSA independently from the body weight. Insulin resistance, type II diabetes and altered serum lipid profile, widely described in patients with OSA, can represent a further risk of cardiovascular morbidity.[31][46]

There is now little doubt that an increased mortality occurs in patients with untreated sleep apnea compared with healthy controls. [47][48] First-line treatments for bipolar disorder include lithium and valproic acid supplemented by use of atypical antipsychotics, all of which are associated with myriad multisystem side effects, especially weight gain, that predispose patients to obstructive sleep apnea (OSA) among other potential complications.[49][50] It has been also seen that serotonergic agonists positively regulate central respiratory drive and increase airway diameter. Therefore, inhibition of this serotonin pathway is suggested to worsen OSA by increasing upper airway resistance.

The main finding of this study was the discovery of a higher incidence of OSA in male patients with BD after adjustment for baseline demographics and co-morbidities. The stratification analysis by sex also revealed that the risk trend with BD and subsequent OSA was mainly contributed by male BD patients and female BD patients weakened the overall association. There are a number of sex differences that could explain the above results.[51]

For example, the activity of the dilator muscles of the upper respiratory tract may be increased in women, making the closure of the upper airway less likely to occur during sleep. In addition, fat deposition in the upper respiratory tract (e.g., lateral parapharyngeal fat pads) is greater in men than in women.

Since OSA has important effects on a patient's cognitive well-being, work performance, and quality of life and this condition can result in pulmonary hypertension, which can be further complicated by acute hypoxemic respiratory failure, cor pulmonale, and death, therefore it becomes imperative that we screen for OSA in patients BD.

Limitations:

1) Given the cross-sectional design of the study, we could not ascertain whether the onset of apnea risk followed or preceded the onset of BD.
2) The present study was based on validated self-report screening questionnaire and the patients who were screened to be at high risk were not subjected to PSG, which is the gold standard for diagnosing OSA.
3) Our finding are applicable to BD patients in Kashmir only and can't be generalized
4) Purposive sampling and single centre study may also bias the results

CONCLUSION:

Patients with BD had significantly higher BMI in comparison to controls. In comparison to controls, significant higher percentage of patients with BD had higher risk for OSA in comparison to healthy controls. Our finding of over half of patients being in the high risk range should be sufficient to sensitize clinicians and raise awareness concerning OSA in BD. Future research should address whether lifestyle and biological factors specific to BD are responsible for the increased risk for OSA. Moreover, given the evidence that patients at risk for sleep-disordered breathing have increased mood symptoms, longitudinal studies that investigate the probable reciprocal interaction between mood and OSA are needed.

In summary, considering the substantial overlap between symptoms of OSA and symptoms of depression and the potentially harmful effects of sleep disruption in patients with mood disorders, a systematic screening to assess the prevalence and associated features of OSA in patients with BD is clearly warranted.

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Conflict of interest
There are no conflicts of interest

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