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Original Research Article

Insomnia & Serum Cortisol level in Major Depressive Disorder

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Abstract: A total of 207 subjects (101 cases of depression & 106 age & sex matched controls) were studied by measuring Athens Insomnia scale (AIS) and serum cortisol**.** Among 101 cases of depression, 19 cases were of mild grade, 37 were of moderate and 45 were suffering from severe depression. It has been found that 91 out of 101 MDD cases had AIS score ≥ 6. Thus the prevalence of insomnia was calculated to be 90.1%.Mean concentration of cortisol was found to be 10.2 ± 5.5 and 6.8 ± 1.6 µg/dl and AIS score was found to be 11.5 ± 4.3 & 3.8 ± 1.6 in cases & controls respectively. Both the parameters were found to be statistically significant. The cases were further classified according to severity. The correlation of cortisol and AIS score with severity of depression was assessed by Spearman rank correlation test. AIS score was found to be significantly correlated with depression showing a distinct relationship between insomnia and depression. Serum cortisol level however, was not found to correlate with the severity of depression.
Keywords: Major Depressive Disorder (MDD), Insomnia, serum cortisol, Athens Insomnia Scale (AIS)

INTRODUCTION

Sleep disorder in form of Insomnia is one of the most common features of depression and the intimate nexus between sleep and depressive symptoms have been studied elaborately. Epidemiological studies show that symptoms of sleep disturbances precede an episode of depression in 40% of cases. It has been observed that people suffering from depression with prominent insomnia are likely to have a poorer response to treatment. Insomnia is also found to be predictive of a greater risk of suicidal behavior [1].

A distinct circadian rhythm is observed in humans, which determine multiple biological and behavioral processes performed by them. One such biological process is sleep which follows a diurnal pattern. This diurnal pattern plays a key role to adapt a person to environmental circumstances. Adaptation to extrinsic and intrinsic forces is a survival necessity for all living organisms. The hypothalamic-pituitary-adrenal (HPA) axis is an adaptive system with the purpose of maintaining a dynamic equilibrium or homeostasis in a constantly changing environment. Sleep is regulated by the HPA axis in multiple ways, and a growing body of research suggests reciprocal associations between sleep and the activity of the HPA axis [2].

It has been observed that a similar diurnal pattern exixts in the stress response, which may be of particular relevance to stress related disorders such as depression. This observation is further enforced as almost 40–60% of patients suffering from depression have been found to have a disturbance in the hypothalamic-pituitary-adrenal (HPA) axis, which manifest as changes in patterns of diurnal cortisol release [3].

The hypothalamus first manufactures corticotrophic-releasing hormone (CRH), which stimulates pituitary gland to release adrenocorticotrophic hormone (ACTH). This hormone then makes the adrenal glands to secrete cortisol in the blood. In normal condition, the hypothalamus monitors

the level of cortisol in the blood. When the level rises, the hypothalamus slows down the production of CRH. When cortisol levels become reduced, the hypothalamus stimulates the pituitary gland to produce more CRH. But in a person who is depressed, the hypothalamus may continuously influence the pituitary to produce CRH without regard to the amount of cortisol present in the blood [4].

In this backdrop, this study was undertaken to find out

1. Prevalence of Insomnia in patients suffering from Major depressive disorder (MDD).
2. To estimate serum cortisol level and Insomnia score in patients suffering from MDD.
3. To find out correlation of serum cortisol level and Insomnia score with MDD.

MATERIALS & METHODS

This Case control study was undertaken inDepartment of Biochemistry, College of Medicine &SagoreDutta Hospital in collaboration with Department of Psychiatry of same Institute. The study period was from June, 2014 to Dec, 2015. The study was approved by Institutional Ethics Committee.

Selection of study subjects

All patients who were suspected to suffer from Major depressive disorder (MDD) were selected from the Psychiatry outdoor of College of Medicine &SagoreDutta Hospital. These patients were first evaluated by detailed history taking and clinical examination through a structured proforma designed for this study. Then they were screened with WHO Five well being index. The raw score was calculated. When raw score was below 13 or if the patient had answered 0 to 1 to any of the 5 items, they were further tested. Patients were diagnosed as having major depressive disorder according to the Structured Clinical Interview for DSM-IV [5] and who scored at least 14 points on Major Depression Inventory (MDI). This inventory was also used to classify the patients according to ICD 10 criteria for depression [6].

The exclusion criteria were significant psychiatric co-morbidity, organic mental disorder, mental retardation, bipolar disorder, intake of any psychotropic drugs during and at least 1 week before the study, substance abuse, history of endocrine disorders, pregnancy, postpartum depression, lactation, and any condition other than depression-related insomnia.

Apparently healthy age and sex matched individuals were assessed using General Health Questionnaire (GHQ 12). A score of less than or equal to 15 were considered as not to suffer from major psychiatric illness [7]. Such individuals were selected as control group.

Informed consents were taken from the patients or legal guardians and from the control subjects. Insomnia was detected using Athens Insomnia scale (AIS 8)from all study subjects (cases & controls) to find out sleep disturbance in whole study population. AIS 8 are a self report questionnaire containing 8 items and designed to measure the severity of insomnia. The first 5 items aim to measure sleep induction, awakening during night, final awakening, total sleep duration, and general sleep quality. Remaining 3 items refer to consequences of insomnia during the following day, specifically, wellbeing, functional capacity and sleepiness. All these 8 factors are rated on a 0 – 3 scale and the sleep is finally evaluated from the cumulative score of all factors. A cut off score of > 6 is considered as insomnia [8].

Sample Collection, Separation & analysis of serum

An amount of 5 ml of fasting blood samples was drawn aseptically from the superficial veins of each of the study subjects (Both cases & controls) in plain vials and allowed to clot. Serum was separated at room temperature and later by centrifugation at 800 g for 10 minutes. Separated serum was kept in refrigerator in aliquots to the maximum for 1 week. Serum of all patients and controls included were investigated for Cortisol concentration by ImmunoEnzymometric assay [9].

STATISTICAL ANALYSIS

The parameters, cortisol concentration & AIS were expressed in mean ± SD. The mean values were compared for significance by student's t test. A p value of <0.05 was considered to be significant.The correlation of AIS & Cortisol with severity of depression was assessed by Spearman rank Correlation test. The analysis was done using Free Statistics Software (v1.1.23-r7), Office for Research Development and Education, (URL http://www.wessa.net/rwasp_correlation.wasp/)

RESULT

A total of 212 subjects (106 cases of depression & 106 age & sex matched controls) were enrolled for the study. Among the 106 patients, 4 patients did not turn up for blood collection and 1 patient did not give consent for the study. Thus a total of 101 cases suffering from depression (Male: 24, female: 77) and 106 (Male: 30, female: 76) controls were studied. Among all depression cases, 19 cases were of mild grade, 37 were of moderate and 45 were suffering from severe depression.

It has been found that 91 out of 101 MDD cases had AIS score > 6. Thus the prevalence of

insomnia was calculated to be 90.1%.Mean concentration of cortisol was found to be 10.2 ± 5.5 and 6.8 ± 1.6 µg/dl and AIS score was found to be 11.5 ± 4.3 & 3.8 ± 1.6 in cases & controls respectively. Both the parameters were found to be statistically significant. The cases were further classified according to severity. Concentration of cortisol and AIS were calculated in each grade, and shown in Table 1.The correlation of cortisol and AIS score with severity of depression was assessed by Spearman rank correlation test, the results of which are shown in Table 2. AIS score was found to be significantly correlated with depression.

Table 1: Serum cortisol and Insomnia score in study population

Study population	Serum Cortisol (µg/dl)	Insomnia score (by AIS)
Control (n = 106)	6.8 ± 1.6	3.8 ± 1.6
Cases (n = 101)	10.2 ± 5.5*	11.5 ± 4.3*
Mild (n = 19)	8.9 ± 4.9	7.7± 3.6*
Moderate (n = 37)	10.5 ± 6.6*	10.5 ± 3.8*
Severe (n = 45)	10.6± 4.7*	13.8 ± 3.6*

All results are expressed in mean ± SD; *p < 0.05, when compared by Student t test

AIS: Athens Insomnia Scale

Table 2: Estimation of correlation coefficient of AIS & Cortisol with MDD

Parameter	Spearman rank Correlation coefficient	T value	P value
AIS vs MDD	0.5354	6.31	p<0.000001*
Cortisol vs MDD	0.1840	1.86	p= 0.065854

***Statistically Significant**

DISCUSSION

Sleep and depression interact in a complex manner. Insomnia has been found to increase the vulnerability to depression, numerous sleep abnormalities are linked to depressive illness, including decreased REM latency, decreased sleep continuity, decreased slow-wave sleep (SWS), increased REM percentage, decreased sleep efficiency, and increased wakefulness. More than 8 epidemiologic studies have shown that insomnia symptoms at baseline predict an increased risk for depression at follow up, anywhere from 1 to3 years later [10]. Typical sleep symptoms in depression include, difficulty initiating sleep (initial insomnia), difficulty maintaining sleep (mid insomnia), and early morning waking (terminal insomnia). Hypersomnia is a pattern that is part of the 'signature' of bipolar depression [11]. In our study, prevalence of insomnia was found to be 90.1%, which is quite high. Insomnia score was also found to be significantly higher in depression cases.

Moreover, grade wise analysis shows that Insomnia score is significantly elevated in mild, moderate and severe depression. Sleep deprivation has a stimulatory effect on the HPA axis, which causes hyper secretion of CRH. This results in increased cortisol levels in plasma, urine and CSF. Exaggerated cortisol responses to ACTH and enlarged pituitary and adrenal glands also found to occur in individuals suffering from severe mood disorders [12]. One study group showed a significant increase in serum level of cortisol (14.5±3.01µg/dl) in patients with depression than in control group (11.56±1.33 µg/dl).We also found, significantly high level of cortisol in MDD cases. However, the elevated level was not found to be significant in cases with mild depression, but it was found to be significantly elevated in cases with moderate and severe depression. The sample size of group containing patients with mild depression is small (n =19), which may be a reason of such result. It is also possible that in mild cases of depression HPA axis stimulation is not sufficient enough to cause significant rise in cortisol level.

The neuro-endocrine studies are mainly focused on the elevation of cortisol in serum and in the saliva[13–15].

However, correlation analysis (Table 2) shows that Insomnia can be significantly correlated with severity of depression but serum cortisol does not. Maes*et al.;* suggested that about 50% of patients with major depression hyper secrete cortisol, but the rate depends on the population sampled [16]. The findings of Strickland *et al.;*[17] suggested that increased cortisol secretion is not a characteristic feature of depression in the community. Moreover, Julia Ross observed that there are 3 biochemical causes of insomnia in depression. First is deficiency of serotonin or dopamine, second is, deficiency of GABA and third is excess of cortisol. Thus excess cortisol is not the only condition that is associated with Depression [18]. Individuals differ in response to stress and adversity, which is also a determining factor for the level of cortisol in blood.

CONCLUSION

Insomnia is considered as a cause as well as one of the manifestations of Depression. It appears that HPA axis over activity which is found in stressful events can exert its effect by increased release of cortisol as well as altering sleep pattern. Reducing cortisol levels and stabilizing HPA axis dysfunction can be a very effective approach to control patients with insomnia and depression.

LIMITATION

In addition to Serum cortisol level, Dexamethasone Suppression test could be done for better assessment of the secretion pattern of cortisol in Depression. But due to infra structural constrain, it could not be done.

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