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Hormonal and Immunological Alteration in Adults Suffering from Depression: a cross sectional study in West Bengal

Psychiatry

KEYWORDS: Depression , CES-D scale , CRP, TSH and prolactin

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ABSTRACT

Depression is a common mental disorder, with an estimated global burden of 350 million. Our study aimed to evaluate the levels of CRP , thyroid stimulating hormone and Prolactin in adult patients with minor depression classified by CES- D scale. The study was conducted on 65 individuals of 35- 55 years with minor depression visiting IPGMER and SSKM Hospital, who give consent and answered the questionaers. We included 65 healthy individuals as control. We observed a significant difference in TSH and prolactin between group D and control ($p<0.001$) and elevated levels of CRP are independently associated with depressive symptoms in group D ($p<0.04$) .An early recognition of an endocrine condition and inflammation may help minimize psychiatric morbidity.

Depression is one of the leading contributors to global burden of disease and the leading cause of disability measured by years lived with disability. Depression is a common mental disorder, with an estimated global burden of 350 million.[1] Unipolar depression ranked fourth in 1990 and could rise to second by 2020 in terms of the overall burden of all diseases in the world.[2]

The actual causes of depression are not currently known. Major depression belongs to a complex group of disorders that manifest diverse clinical symptoms present to varying extents. The following symptoms are characteristic of the disorder: low mood, anhedonia, alterations in body weight not connected with diet, insomnia or hypersomnia, excitement or low motor activity, fatigue, feelings of guilt or/and worthlessness, lower intellectual abilities, lack of concentration as well as an inability to make decisions, and recurrent suicidal thoughts.

Notably, major depression episodes occur twice as frequently in women (20–25%) as in men (7–12%) .The interactions between central nervous system and immune system in depression have a biological explanation supported by the monoamine synthesis.[3]

In depression positive acute phase proteins such as C reactive protein and haptoglobin are increased while negative acute phase proteins like albumin and trasferrin are decreased[4]

C-reactive protein (CRP) is a commonly used marker of inflammatory disease. When used to study low-grade inflammation and future risk for disease, CRP levels are measured with a high-sensitivity assay .Elevated CRP levels have been associated with psychological distress and depression, but results are conflicting. [5,6]

Some studies suggest that the existence of a possible "psychoneuro immune link" between negative affectivity (depression, anger and anxiety [7] poor subjective wellbeing [8] inflammatory markers, and the development and progression of CHD[9] Several behavioral and psychosocial factors, particularly depression, appear to increase the risk for acute coronary syndrome events independent of traditional risk factor status.

Increasing interest has recently been shown in the possibility of a connection between Prolactin (PRL) levels and depressive disorders. PRL is supposedly regulated or influenced by a number of factors that are of interest in affective disorders [such as dopamine, norepinephrine, serotonin (5-HT), thyroid hormones, corticosteroids, and calcium.[10]

Anxiety, somatization, hostility and / or depression were, thereafter, related to hyperprolactinemia [11]. There are few published studies on the subject, usually with a small number of patients. These studies do not always exclude other pathologies related to psychological disorders, use variable and sometimes inadequate scales of quantification of psychiatric symptoms and have discordant results regarding the relationship between prolactinemic levels and these symptoms.

Thyroid dysfunctions have been recognized to cause significant manifestations in mental health. They may lead to disturbances in emotions and cognition. Both increase and decrease in thyroid function can cause mood abnormalities. Vice versa, depression can also go hand in hand with subtle thyroid dysfunctions. On the other hand, depression can be accompanied by subtle thyroid dysfunction. Overt thyroid disease is rare in depression. One to 4% of patients with affective disorders are found to have overt hypothyroidism while subclinical hypothyroidism occurs in 4% to 40% of these patients.[12,13] Assessment of the thyroid function tests can be a good predictor in the treatment of depression and bipolar disorders.[14] THs can be used as augmentation agents and are therapeutically efficient in treatment-resistant depression.[15]

The present study aimed to evaluate the levels of CRP , thyroid stimulating hormone and Prolactin in adult ambulatory patients with minor depression in comparison with non depressed subjects.

Materials and methods:

Study subjects:

Between March 2014 to February 2015, 65 individuals of 35- 55 years age group having various symptoms of minor depression visiting IPGMER and SSKM Hospital, Kolkata India were enrolled in the study after considering questioners and exclusion criteria. 65 healthy volunteers were included as a control group.

Study groups:

On the basis of CES –D model the depressive patients were categorized in four groups.

Inclusion criteria :

- Patients of 35-55 years of age
- Patients who gave written consent for study
- Patients gave answers the questioners according CES D scoring and proforma
- Patients clinically diagnosed for depression.

Exclusion Criteria:

- Patients suffering severe psychiatry co morbidity
- Significant co morbid illness
- Pregnant and lactating women

Ethical statement:
Ethics clearance was obtained prior to data collection from the institutional ethics committee IPGMR and SSKM Hospital .Kolkata, India.

Parameters studied:
a) Physical : body weight, Blood pressure, height and BMI
b) Biochemical: Blood sugar (fasting), Urea, Creatinine, CRP, Insulin, TSH and prolactin.

Questionnaire data:
All participants were interviewed by trained personnel using standardized questionnaires according to the pre developed protocol.

Sociodemographic variables included age, education and marital status (with or without spouse). Health behaviors included smoking status, alcohol intake and sleep duration. Sleep duration was collected in hours per day (h/day) as the average during the past year. The presence of co morbidities were assessed by self-report and if doctor's prescription available.

The CES-D items were selected from a pool of items from previously validated depression scales[16]. The 20-item CES-D Scale measures the experience of depressive symptomatology during the past week. The measure was developed from items appearing on longer, well-validated depression scales.

The items assess cognitive, affective, behavioral, and somatic symptoms of depression, and positive affect. Each item is rated on a 4-point scale ranging from 0 = rarely or none of the time (less than 1 day) to 3 = most or all of the time (5-7 days). A total score is calculated by summing the responses after reversing the positive affect items. Higher scores reflect greater levels of depressive symptomatology.

1. I was bothered by things that usually don't bother me.
2. I did not feel like eating; my appetite was poor.
3. I felt that I could not shake off the blues even with help from my family or friends
4. I felt that I was just as good as other people.
5. I had trouble keeping my mind on what I was doing.
6. I felt depressed.
7. I felt that everything I did was an effort.
8. I felt hopeful about the future.
9. I thought my life had been a failure.
10. I felt fearful.
11. My sleep was restless.
12. I was happy.
13. I talked less than usual.
14. I felt lonely.
15. People were unfriendly.
16. I enjoyed life.
17. I had crying spells.
18. I felt sad.
19. I felt that people dislike me.
20. I could not get "going."

Sample collection:
Standing height was measured to the nearest 0.1 cm using a stadiometer and body weight was measured to the nearest 0.1 kg on a digital scale. Body mass index (BMI) was calculated as body weight in kilograms divided by standing height in metres squared (kg/m^2).

Blood samples were collected from the antecubital vein of participants after at least 8 h of fasting. Using aseptic precautions 4ml of venous blood samples were collected in red capped vaccutainer and were used for estimation of CRP , TSH and Prolactin.

Method of estimation of CRP , TSH and Prolactin :
TSH and prolactin were assessed by ELISA method.
CRP was measured using latex enhanced turbidimetric immunoassay.

Statistical analysis:
Data was compiled and statistical evaluation was done using Statistical Package for the Social Sciences (SPSS) 16.0. Data were expressed as mean± standard error. ANOVA was used for comparison between groups. *P* value <0.05 is considered as statistically significant.

Results :
Demographic characteristics of the study participants are presented in Table 1.

Table 1. Demographic characteristic of the study groups

SCORING	CES- D	Number of subject	Sex Ratio (M:F)	Mean Age	BMI (Mean ± SD)	Smoking
≤ 16	A	12	1:2	45	25.72 ± 5.18	13%
16 – 32	B	16	1:1	48	26.3 ±4.12	15%
32-- 48	C	21	2:3	50	29.9 ± 2.08	25%
48 --64	D	16	1:2	51	28.72 ± 3.17	20%
	Control	65	3:2	47	24.8 ± 3.91	30%

We found more female patients with depression than male. Group C and D had more overweight patients than healthy control. We didn't find any significant correlation with smoking habit.

Table 2: Showing hormonal levels in different groups

CES --D	TSH (MEAN ± SE) µIU/ml	Prolactin (MEAN ± SE) ng/ml
A (n=12)	3.01 ± 0.55	7.41 ± 0.85
B (n=16)	5.04 ± 0.68	8.58 ± 0.62
C (n=21)	5.33 ± 0.37	9.59 ± 0.61
D (n=16)	11.74 ± 1.34	15.2 ± 0.23
CONTROL (n=65)	3.31 ± 0.14	9.28 ± 0.42

We observed a significant difference in TSH and prolactin between group D and control ($p<0.001$)

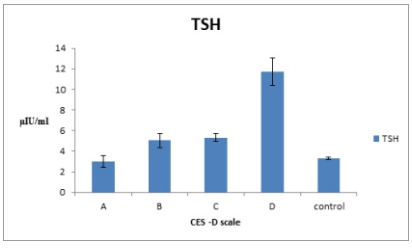

Fig 1: Bar diagram showing TSH levels in different groups

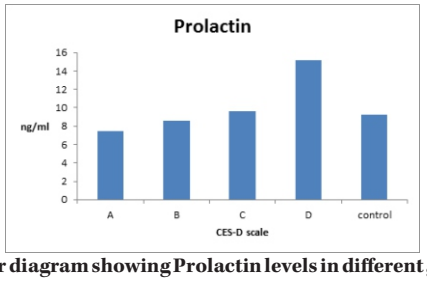

Fig 2: Bar diagram showing Prolactin levels in different groups

Our findings suggest that elevated levels of CRP are independently associated with depressive symptoms in group D ($p<0.04$).

Table 3: Showing the Fasting blood sugar and C reactive protein

CES --D	FBS (MEAN ± SD) mg/dl	CRP (MEAN ± SE) mg/L
A (n=12)	89.12 ± 11.17	0.17 ± 0.029
B (n=16)	92.76 ± 15.7	0.28 ± 0.027
C (n=21)	98.78 ± 12.01	0.32 ± 0.031
D (n=16)	126.10 ± 16.31	0.68 ± 0.048
CONTROL (n=65)	86.67 ± 11.71	0.22 ± 0.032

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Discussion

This study investigated serum CRP levels, TSH and prolactin in adult depressive patients.

Our results are consistent with previous findings linking elevated CRP levels to depression[17].

The relationship between inflammation and depression is potentially bidirectional, and the underlying mechanisms are still poorly understood. First, inflammation may lead to depression. Increased inflammatory markers contribute to decreases in serotonin, an important neurotransmitter in the pathogenesis of depression.[18] Second, depression may lead to inflammation. Psychological stress activates the sympathetic nervous system and releases stress hormones. These hormones in turn initiate acute-phase responses triggering inflammation.

We found hypothyroidism in group D patients TSH value (11.74 ± 1.34). However, the distribution of subclinical hypothyroidism is more in group B and C.

The results of the study by Thvilum *et al.*[19] showed that the patients with hypothyroidism are at increased risk of being diagnosed with psychiatric disorders both before and after the diagnosis of hypothyroidism and being treated with antidepressants, antipsychotics, as well as anxiolytics. Kalra and Balhara [20] had suggested that thyroxine replacement as a monotherapy fails to achieve total remission.

Findings of our study suggest the need for inclusion of few more other related thyroid markers T3, T4 and FT4, along with TSH level monitoring, so as to obtain even more accurate and reliable information on thyroid status of the depressive patients for their proper diagnosis and treatment.

Our study showed group D tended to have higher basal PRL concentrations than control but the values are within reference range.

Papakostas and colleagues recently reported that 4.5% of men and 22.2% of women with major depressive disorder (MDD) developed new-onset hyperprolactinemia following treatment with fluoxetine[21] The study has some limitations. First, since this is a cross-sectional study in which all information was collected at the same point in time, no definitive conclusion about the direction of the associations between CRP levels,TSH , prolactin anddepressive symptoms could be reached. Second, we relied on a single blood sample per individual. Inflammatory markers other than CRP were not measured in this study. Further studies including other inflammatory markers,fT4, needed to confirm our results. Fourth, we investigated depressive symptoms using the CES-D scale, which has been widely used to assess depression and its risk factors in population-based studies.

Clinical implications

- For endocrinologists: Any patient on treatment for hypothyroidism and not improving must be screened for depression and anxiety symptoms using any of the rating scales and managed accordingly.
- For psychiatrists: Any patient seeking treatment for either depression or anxiety, not responding to standard dosages of medication or requiring more than usual dosages of the psychotropic drugs, should be screened for the thyroid and prolactin status.. If in case of a single isolated elevated TSH level in a depressed patient, he/she should be treated with a rational approach[23]

TSH play an important role in mood and behavior, and cognition is an established entity. Thus, the correlation between psychiatry disorder and thyroid status is a major area of concern. Furthermore, thyroid dysfunctions can lead to psychiatric co morbidities such as depressive disorder, anxiety disorder, and disturbances in memory and learning also hold true.

In conclusion, our findings suggest that high serum CRP levels are independently associated with depressive symptoms .Chronic inflammation may be another possible risk factor for depressive symptoms[24].

The patient's presenting with such sign and symptoms should be monitored and treating by both an endocrinologist and a psychiatrist in liaison with each other so as to optimize their management. Moreover, an early recognition of an endocrine condition will help minimize psychiatric morbidity and hence improve health. Further studies are needed to establish a causal relationship between inflammation and depression and to investigate the underlying mechanisms.

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