Evaluation of Endocrine Parameters as Predictor of Major Depressive Disorder

Soma Gupta, Amrita Mukherjee¹, Sangita Biswas¹, Smarajit Bose², Saswati Nath³, Harendra Nath Das¹

ABSTRACT

Background: The diagnosis of the disease, major depressive disorder (MDD), entirely depends on the presence of some symptoms without any biochemical parameter to support it. Depletion of dopamine though is an established feature, is not the sole causative factor of MDD. Moreover, it has very little diagnostic value due to a short half-life. Other chemical messengers like hormones have also been found to get altered due to significant over activity of hypothalamo-pituitary axis. Literature review suggests that cortisol, thyroid-stimulating hormone (TSH), and prolactin (PRL) are mostly altered in MDD, which can be utilized to diagnose the condition.

Materials and Methods: A total of 101 patients suffering from MDD along with 106 age- and sex-matched controls were included in this study. Cortisol, TSH, and PRL were assayed in all the study participants by enzyme immunoassay. Student’s t-test and linear discriminant analysis were used for statistical analysis.

Results: All the three hormones were found to be significantly high in cases with MDD. When applied for classification purpose, the errors in training group were found to be 15% and 15.74% from test set. None of the normal population was wrongly diagnosed as a patient of depression.

Conclusion: To the best of our knowledge, this is the first attempt to evaluate multiple biochemical parameters as diagnostic marker of MDD. The study is in progress to find out a cutoff value of the responsible parameter so that they can be optimally used to diagnose a case of MDD.

Key words: Cortisol, major depressive disorder, prolactin, thyroid-stimulating hormone

INTRODUCTION

Major depressive disorder (MDD), though is a leading cause of disability along with an alarmingly increased global prevalence, its pathophysiology is yet not established clearly.

The monoamine theory of depression¹ suggested that depression was a consequence of diminished neurotransmission involving monoamines, namely, serotonin, dopamine, and norepinephrine. The decrease in their concentrations or reduced sensitivity to their

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.
actions on receptors was proposed to be responsible for the symptoms of depression. However, the biochemical changes found in depression have not been explained only by this model or theory. Moreover, estimation of these neurotransmitters is difficult, and thus their use as a diagnostic tool in depression is limited. A study from Pum[1] showed that there is no clinical significance of estimating norepinephrine, epinephrine, or dopamine in depression. They concluded that norepinephrine neither appears to critically differentiate between different types of depressive illness nor it seems to act as a surrogate parameter to indicate clinical improvement in mentally depressed patients.

Among other theories, the neuroendocrine hypothesis is gaining importance. This theory states that pathological mood states are explained or contributed to by altered endocrine function. This theory historically grew out of observations that altered mood states were associated with thyroid or Cushing’s disease.

Another theory, the diathesis–stress model[4] tries to combine these both theories. According to this model, depression results when a preexisting vulnerability, or diathesis, is activated by stressful life events. Stressors are different types such as “social stress” and “physical stress.” Humans respond to stress through activation of the hypothalamic-pituitary-adrenal (HPA) axis. This activation results from the activation of corticotropin-releasing factor outside the hypothalamus and activation of sympathetic nervous system through adrenalin or noradrenaline. Chronic elevation of glucocorticoids inhibits dopamine synthesis and its turnover in the nucleus accumbens. Chronic stress also results in exhaustion of catecholamines (norepinephrine and epinephrine). Central catecholamine depletion occurs in this disorder which is known to have a stimulatory effect on prolactin (PRL) secretion.[5]

Cortisol and thyroid-stimulating hormone (TSH), though studied widely in MDD, study on PRL is comparatively less. However, if the diathesis–stress model is considered as the key factor in the pathogenesis of MDD, all these three hormones seem to get altered.

Hence, this study was undertaken with the following objectives:

- To find out whether there is any significant alteration of these three hormones in MDD
- Whether people can be successfully classified into depression and normal groups using these parameters.

MATERIALS AND METHODS

This case–control study was undertaken in the Department of Biochemistry, College of Medicine and Sagore Dutta Hospital and R. G. Kar Medical College in collaboration with the Department of Psychiatry of both institutes. The study period was from July 2013 to December 2015. The study was approved by the Institutional Ethics Committee.

Selection of study subjects

All patients who were suspected to suffer from MDD were selected from the psychiatry outdoor of College of Medicine and Sagore Dutta 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 the WHO-5 Well-Being Index. The raw score was calculated. When raw score was below 13 or if the patient had answered 0–1 to any of the five items, they were further tested.[6] Patients were diagnosed as having MDD according to the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[7] and who scored at least 14 points on Major Depression Inventory (MDI). This inventory was also used to classify the patients according to the International Classification of Diseases, Tenth Edition criteria for depression.[8]

The exclusion criteria were significant psychiatric comorbidity, 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, and postpartum depression and lactation.

Apparantly healthy age- and sex-matched individuals were assessed using General Health Questionnaire-12. A score of ≤15 was considered as not to suffer from major psychiatric illness.[9] Such individuals were selected as control group.

Informed consents were obtained from the patients or legal guardians and from the controls.

Gradation of major depressive disorder cases

MDI score of 20–24 was considered as mild grade, 25–29 as moderate grade, and ≥30 was considered as a severe grade.[10]

Sample collection, separation, and analysis of serum

An amount of 5 ml of fasting blood samples was drawn aseptically from the superficial veins of each of the study participants (both cases and controls) in plain vials and allowed to clot. Serum was separated at room temperature and later by centrifugation at 800 g for 10 min. Separated serum was kept in refrigerator in aliquots for maximum 1 week. Serum of all patients and controls included were investigated for cortisol, TSH, and PRL by immunoenzymometric assay.[11-13]
**Statistical analysis**

The mean values were compared for significance using the Student’s *t*-test. *P* < 0.05 was considered statistically significant.

The patients were further subdivided in mild, moderate, and severe grade. One-way analysis of variance with *post hoc* test is used to test the difference between the means of several subgroups.

Linear discriminant analysis (LDA) was used to find out whether the two population can be classified using these parameters. For LDA, fifty normal and fifty patients among the study population were randomly selected to create a training sample. The rest of the cases were kept aside as independent test cases to evaluate future prediction error. The method assumes that the predictors have multivariate normal distribution for both populations. Moreover, the means are different, but the variance–covariance matrices are the same for the two populations. Based on the training set observations, the means and the common variance–covariance matrix are estimated. Prediction errors are estimated using the independent test set.

**RESULTS**

The collected data have 101 MDDs (77 female and 24 male), and 106 age- and sex-matched healthy people (76 female and 30 male). Among 101 patients, 19 were mild grade, 37 were moderate grade, and 45 were severe grade.

Table 1 shows the mean level of endocrinial parameters, namely, cortisol, TSH, and PRL along with their standard deviations in study groups. All the parameters were found to be significantly increased. Table 2 shows the level of endocrine parameters in different grades of MDD. None of them were found to be significantly altered. Table 3 shows LDA of data set. The errors in training group were found to be 15% and 15.9% errors were observed in the test group (overall error being 15.4%).

**DISCUSSION**

Developments in the field of neuroendocrinology have highlighted the significance of endocrine systems in the etiology and pathogenesis of mood disorders.

Stressful life events stimulate HPA axis, the end product of which is cortisol. Elevated cortisol levels can lower brain 5-HT (serotonin) function and this, in turn, leads to the manifestation of the depressive state. Increase in cortisol level in patients with depression is reported by several study groups and it is more or less a consistent finding. We also found a significant increase in the level of cortisol.

Serotonin is known to inhibit thyrotropin-releasing hormone (TRH) constantly. Reduced intracerebral serotonin which is an important factor to develop MDD leads to increased TRH concentrations in brain tissue. As a consequence, TSH secretion gets stimulated.

While considering the levels of TSH in depressive patients in comparison to the controls, it was found to be significantly higher in the depressive group. It is in agreement with many previous studies.

Another hormone found to be significantly increased in MDD patients in our study is PRL. Horrobin proposed that PRL can be increased in MDD, but Arana et al. did not observe any significant alteration of PRL level in patients with mild depression. It should be kept in mind that determination of PRL level in a single blood sample does not reflect the entire 24-h pattern of PRL secretion, which can be considered as a limitation of the study.

TRH is not only known to stimulate TSH but also PRL. Within the brain, PRL acts as a neuropeptide to promote
physiological responses related to reproduction, stress adaptation, neurogenesis, and neuroprotection. PRL was found to reduce neurogenesis, when administered, during the early developmental stages and promotes depressive-like behavior in adulthood. Some of these effects are mediated by the activation of different neuronal signaling systems and ion channels.[20] Grade-wise classification of depression did not show any statistical significance for either of the hormone. This may be due to inequality of sample size in three groups with inadequate number of data in the mild group.

To the best of our knowledge, this study is the first attempt made to diagnose MDD cases with the combined estimation of three hormones. Considering these three endocrinological parameters together, 15% of the patients with MDD could not be correctly diagnosed from training set and 15.74% from test set. None of the normal population was wrongly diagnosed as a patient of depression.

CONCLUSION

Hormones and neurotransmitters share common pathways and receptor sites in areas of the brain linked to depression. Cortisol, TSH, and PRL are important hormones to get significantly altered in depression. Grade-wise classification of depression did not show any statistically significant alteration for either of the hormone.

Combined estimation of these three hormones can approximately misdiagnose 15.4% of the patients with MDD. Further analysis on increased sample size may minimize the error, and some biochemical parameters might be available to diagnose MDD patients.

Acknowledgment

The authors would like to acknowledge the support and help of Late. Dr. Swati Bera, Associate Professor, Department of Biochemistry, R. G. Kar Medical College. The support of the West Bengal University of Health Sciences is also duly acknowledged.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Schildkraut JJ. Biogenic amines and affective disorders. Annu Rev Med 1974;25:333-48.
2. Ambade V, Arora MM, Singh P, Somani BL, Basannar D. Adrenaline, noradrenaline and dopamine level estimation in depression: Does it help? Med J Armed Forces India 2009;65:216-20.
3. Carroll BJ, Curtis GC, Mendels J. Neuroendocrine regulation in depression. II. Discrimination of depressed from nondepressed patients. Arch Gen Psychiatry 1976;33:1051-8.
4. Lazarus RS. From psychological stress to the emotions: A history of changing outlooks. Annu Rev Psychol 1993;44:1-21.
5. Pitchot W, Herrera C, Anseau M. HPA axis dysfunction in major depression: Relationship to 5-HT (1A) receptor activity. Neuropsychobiology 2001;44:74-7.
6. Monroe SM, Simons AD. Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. Psychol Bull 1991;110:406-25.
7. First MB, editor. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
8. Bech P, Rasmussen NA, Olsen LR, Noerholm V, Abildgaard W. The specificity and sensitivity of the Major Depression Inventory, using the present state examination as the index of diagnostic validity. J Affect Disord 2001;66:159-64.
9. Gokilberg D. Identifying psychiatric illnesses among general medical patients. Br Med J 1985;291:161-2.
10. Olsen LR, Jensen DV, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychol Med 2003;33:361-6.
11. Burtie CA, Ashwood ER, editors. Tietz Fundamentals of Clinical Chemistry. 5th ed. Philadelphia: WB Saunders; 2001. p. 862.
12. Hopton MR, Harrop JS. Immunoradiometric assay of thyrotropin as a “first-line” thyroid-function test in the routine laboratory. Clin Chem 1986;32:691-3.
13. Schulster D, Gaines Das RE, Jeffcoate SL. International standards for human prolactin: Calibration by international collaborative study. J Endocrinol 1989;121:157-66.
14. Dinan TG. Glucocorticoids and the genesis of depressive illness. A psychobiological model. Br J Psychiatry 1994;164:365-71.
15. Cowen PJ. Cortisol, serotonin and depression: All stressed out? Br J Psychiatry 2002;180:99-100.
16. Gold MS, Pottash AL, Extein I. Hypothyroidism and depression. Evidence from complete thyroid function evaluation. JAMA 1981;245:1919-22.
17. Horrobin DF. Prolactin and mental illness. Br J Psychiatry 1974;124:456-7.
18. Arana G, Boyd AE 3rd, Reichlin S, Lipsitt D. Prolactin levels in mild depression. Psychosom Med 1977;39:193-7.
19. Sassin JF, Frantz AG, Weitzman ED, Kapen S. Human prolactin: 24-hour pattern with increased release during sleep. Science 1972;177:1206-7.
20. Torner L. Actions of prolactin in the brain: From physiological adaptations to stress and neurogenesis to psychopathology. Front Endocrinol (Lausanne) 2016;7:25.