A Tale of Two Bivalent Cations in Major Depressive disorder

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Abstract
The level of calcium and magnesium was estimated in 150 cases of Major Depressive Disorder (MDD) along with age and sex matched 150 control subjects. The level of magnesium was found to be decreased statistically. This finding was also consistent when the cases were graded according to the severity. This simple test can easily be used in diagnosis of MDD cases and supplementation in necessary cases may be helpful for the patients.

Keywords: Major Depressive Disorder, Calcium, Magnesium

Introduction
Numerous factors are known to contribute in pathogenesis of Major Depressive Disorder (MDD), among which nutritional status of vitamins and minerals were found to play important role as they are involved in different metabolic regulations. A study on adult men reported that supplement of oral multivitamins in combination with calcium, magnesium, and zinc had an effect on relieving anxiety and perceived stress (1). Neuronal deficits of Magnesium ion were also found to be induced by stress hormones, excessive dietary calcium as well as dietary deficiencies of magnesium. Cernak et al. (2) showed that chronic stress decreases both free and total plasma ionized magnesium and simultaneously increased oxidative stress in humans. The mechanism can be understood by the fact that Magnesium ions regulate calcium ion flow in neuronal calcium channels, helping to regulate neuronal nitric oxide production. In magnesium deficiency, neuronal requirements for magnesium may not be met, causing neuronal damage, which could manifest as depression. Magnesium treatment is hypothesized to be effective in treating major depression resulting from intraneuronal deficits. Eby & Eby suggested magnesium deficiency as cause of Major Depressive Disorders and recommended immediate, wide-spread further study on it. Considering the facts that there is an increasing trend of prevalence of depression, throughout the world including India and there is no known biochemical parameter to diagnose the condition, this simple test may have an enormous importance to public health (3).
Aims & Objectives

1. To estimate serum level of Calcium and magnesium in patients suffering from MDD.

2. To find out whether these parameters have any significant difference when the disease is classified according to grade.

Materials and Methods

This Case control study was undertaken in Department of Biochemistry, College of Medicine & Sagore Dutta Hospital in collaboration with Department of Psychiatry of same Institute. The study period was from July, 2013 to Feb, 2016. The study was approved by Institutional Ethics Committee.

I. 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 & 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 WHO Five well being index (4). 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, and who scored at least 14 points on Major Depression Inventory (MDI) (5). This inventory was also used to classify the patients according to ICD 10 criteria for depression.

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

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 (6). Such individuals were selected as control group.

Informed consents were taken from the patients or legal guardians and from the control subjects.

II. Gradation of MDD cases

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

III. Sample Collection, Separation & analysis of serum

An amount of 5 ml of fasting blood samples was drawn from each of the study subjects (Both cases & controls). Serum was separated and was analysed using metal complexing dye cresophthalein for calcium (7) and calmagite for magnesium (8).

IV. Statistical Analysis

The concentration of Calcium and magnesium were expressed in mean ± SD in both the study groups. The mean values were compared for significance by student’s t test. A p value of <0.05 was considered to be significant.

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

The analysis was done using Analyse it Standard edition software version 4_80_9.

Results

A total of 300 subjects (150 cases of MDD, along with 150 age and gender matched control) were included in the study. All cases were further classified according to the severity into mild, moderate and severe grade. Age and gender distribution of each grade is shown in Table 1.
Table 1: Grade wise Age & Gender distribution of cases with Major Depressive Disorder

| Grade        | Female | Male | Mean age |
|--------------|--------|------|----------|
| Mild (n = 36)| 28     | 08   | 23.2 yrs |
| Moderate (n = 55) | 39    | 16   | 28.9 yrs |
| Severe (n = 59)   | 45    | 14   | 49.7 yrs |
| Total (n = 150)  | 112   | 38   | 38.6 yrs |

The mean age of patients of each grade is also calculated. The distribution table clearly shows a female preponderance.

Table 2 shows serum level of calcium and Magnesium in both the study groups. Both the parameters were found to be decreased in cases with MDD but difference was found to be statistically significant only in case of Magnesium.

Table 2: Level of Calcium & Magnesium in Study Groups

| Biochemical Parameter | Statistical Parameter | Case (n = 150) | Control (n = 150) |
|-----------------------|-----------------------|---------------|------------------|
| Calcium               | Arithmetic mean (mg%) | 9.1027        | 9.2751           |
|                       | Standard deviation    | 0.9669        | 0.5625           |
|                       | Standard error of the mean | 0.0789    | 0.0459           |
| Magnesium             | Arithmetic mean (mg%) | 1.6967        | 2.1263           |
|                       | Standard deviation    | 0.5600        | 0.8771           |
|                       | Standard error of the mean | 0.0457    | 0.0716           |

Test statistic t: 1.8876, Two-tailed probability: P = 0.0601
Test statistic t: 5.0561, Two-tailed probability: P <0.0001

Moreover, the decreasing trend of blood magnesium level was found to be consistent, when the level was analysed in each grade. However, In case of calcium the decreasing trend was found to be present in mild and moderate grade only (Table 3).

Table 3: ANOVA test of the study group

| Grade of MDD (n = 150) | Biochemical Parameter | Calcium | Magnesium |
|------------------------|-----------------------|---------|-----------|
|                        | Mean (mg%) ± SD       | F Ratio (significance) | Mean (mg%) ± SD | F Ratio (significance) |
| Mild (n = 36)          | 8.12 ± 0.95           | 0.85 (P = 0.42)       | 1.56 ± 0.64     | 3.02 (P = 0.05)       |
| Moderate (n = 55)      | 9.16 ± 1.02           | 1.64 ± 0.53           |             |                        |
| Severe (n = 59)        | 9.16 ± 0.93           | 1.82 ± 0.50           |             |                        |

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Discussion

The finding of low serum magnesium level is in accordance with the findings of Zieba A et al (9) and Kirov GK et al (10). Magnesium remains in the synapse between two neurons where calcium and glutamate also reside. Calcium and glutamate are excitatory, and in excess, toxic. They activate the N-Methyl-D-aspartate (NMDA) receptors, whereas magnesium is a non-competitive inhibitor of the NMDA receptors. Hence Magnesium deficiency results into Neuromuscular hyper excitability, depression and behavior disturbances (11). A study was done among 16 patients with depression and 12 normal subjects. They found that total plasma magnesium levels were lower among patients, but no difference in levels of ionized magnesium (12). Jung et al assessed serum magnesium levels in 112 healthy adult women without psychiatric disorders and observed that women in the lowest tertile of serum magnesium levels had a higher risk of developing depressive mood disorder (13).

Though depletion of magnesium ions is known to impair control of calcium ions in neuronal channels, change in magnesium ion is supposed to be associated with a change in calcium level. Moreover, studies have reported association of low dietary calcium with depression (14) the normal level of calcium can be explained by the fact that serum calcium homeostasis is dynamic, it appears that the subjects were able to keep their serum calcium concentration level in the normal range with the help of vitamin D and Parathyroid hormone. This mechanism is supported by other study group also (15).

Conclusion

The burden of MDD is showing an increasing trend not only in India but throughout the world.

Magnesium deficiency has been found to be a strong component of the disease. Change in dietary habits, water treatment system, increased use of bottled beverage; all might have been contributed to inadequate intake of magnesium. A simple laboratory test is enough to identify the condition of hypomagnesaemia. Necessary precaution and timely supplementation of magnesium may decrease the incidence of depression. Thus magnesium deficiency as cause of MDD is enormously important and need further study.

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Declaration

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