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A study of serum magnesium and serum calcium in major depressive disorder

Abstract

Background: Depression is arguably the epidemic of our time. In one of the reports of the World Health Organization, it was projected that depression and heart disease will be the most common diseases on Earth by 2020. The paper attempts to determine the relationship between the pathophysiology of major depressive disorder (MDD) and serum magnesium and serum calcium levels. **Methodology:** The study is based on a sample of 60 subjects – 30 healthy normal individuals and 30 indoor and outdoor patients of the Department of Psychiatry of Gauhati Medical College and Hospital, Guwahati, who were identified by psychiatrist as having MDD as per the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Estimation of the parameters of the study was done by using spectrophotometre (Spectra scan UV 2600). The result values of both the groups were compared by using independent 't' test. Further, the correlation between serum magnesium and serum calcium among individuals of control as well as case groups were carried out by using Pearson's correlation test. **Results:** Analysis of data reveals the mean value of serum magnesium among subjects of control group was higher than that of the subjects of the case (before treatment) group while in case of serum calcium, it was the vice versa. Moreover, in both the cases, the differences in mean values were found to be statistically significant. **Conclusion:** The present study shows that alterations in the concentrations of magnesium and calcium may play a role in depressive illnesses and thus, may have a possible role in causing various mood disorders like MDD.

Keywords: N-Methyl-D-Aspartate. Mood Disorders. Nitric Oxide Synthase.

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Introduction

Mood is a pervasive and sustained feeling tone that is experienced internally and influences a person's behaviour and perception of the world. Mood can be normal, elevated, or depressed. Mood disorders encompass a large spectrum of disorders in which pathological mood disturbances dominate the clinical picture. Major depressive disorder (MDD) is the most common and severe mood disorder which can occur alone or as a part of bipolar disorder. It is characterised by a sense of inadequacy, despondency, decreased activity, pessimism, sadness, excessive guilt, depressed mood, anhedonia (absence of pleasure), thoughts of death, and loss of, or increase in appetite. These symptoms severely disrupt and adversely affect the person's life and in extreme situations the victim/patient attempts suicide[1] or dies as a result of such an attempt. Significantly, depression is seen as a serious mental illness with a major impact on both individual as well as family functioning.[2]

MDD is also known as recurrent depressive disorder, clinical depression, major depression, unipolar depression, or unipolar disorder. However, the term '*major depressive disorder*' was selected by the American Psychiatric Association to designate this symptom cluster as a mood disorder in the 1980 version of the Diagnostic and Statistical Manual of Mental Disorders (DSM).[3] Studies show that both magnesium (Mg^{++}) and calcium (Ca^{++}) are cations which occur abundantly in the body and are implicated in numerous cellular functions including regulation of various neurotransmitters.[4] Thus, these two cations do have a role in MDD.

Pathophysiology

The N-methyl D-aspartate (NMDA) receptor, a type of ionotropic glutamate receptor, plays a prominent role within the central nervous system (CNS). NMDA receptors are heteromeric complexes comprising some combination of NR1, the obligatory subunit for a functional receptor and NR2 subunits.[5] This complex forms a channel that has high permeability to Ca^{++} and displays voltage-dependent blockade by Mg^{++} ions.[6] The influx of Ca^{++} through the NMDA receptor can initiate a variety of intracellular second messenger cascades and the precise nature of these second messenger cascades is in large part determined by the amount and duration of the NMDA receptor activation.[7] In the CNS, NMDA-mediated Ca^{++} entry influences widespread events such as gene expression, circuit development, synaptic plasticity, and cell survival.

Most of the brain's regular functions operate quickly and involve the excitatory amino acids glutamate and aspartate in the NMDA receptors. These two amino acids are involved in NMDA nerve cell electrical conduction activity across brain cell synapses, a region hypothesised to function in a quantum mechanics manner.[8] The over-stimulation of the NMDA receptors with glutamate results in a large influx of Ca^{++} into the cell interior, particularly into neuronal mitochondria.

At normal neuronal resting potential, the pores of the glutamate-gated ion channels are blocked by Mg^{++} ions.[9,10] Therefore, Mg^{++} depletion is specifically deleterious to neurons by causing NMDA-coupled Ca^{++} to be biased towards opening of the channels[11] because Mg^{++} acts as nature's Ca^{++} blocker.

The ion channels of the NMDA-receptor complex is subject to voltage-dependent regulation by Mg^{++} ions.[10,12] Normally operating NMDA receptors admit into neurons the amount of Ca^{++} ions that is vital to their function, but abnormally functioning NMDA receptors increase the cellular Ca^{++} ions beyond manageable levels leading to the activation of a series of Ca^{++} dependent enzyme systems. The excess Ca^{++} ions combines with the Ca^{++} binding protein called calmodulin and causing activation of the calmodulin-Ca^{++} dependent enzyme, the neuronal nitric oxide synthase (nNOS).[13] nNOS is a constitutive type of NOS, and activity of the purified enzyme is dependent on Ca^{++}[14] and calmodulin[15] in the presence of cofactors such as flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide phosphate (NADPH), and tetrahydrobiopterin (BH4). The nNOS catalyses the oxidation of L-arginine resulting in the formation of L-citruline and nitric oxide (NO), which is a diffusible, free-radical messenger, involved in cell to cell communication and in numerous neuropsychiatric conditions.[16] The production of NO is a calmodulin-dependent process; therefore, it must be preceded by elevation of intracellular Ca^{++} concentration. Interestingly, nNOS produces NO almost exclusively after activation of the NMDA receptors.[17]

The calcium ions influx through the NMDA receptors is efficiently coupled to the NO synthesis and activity.[18] Following its synthesis at the post-synaptic sites, NO may diffuse back to the presynaptic terminal[19] and increase cyclic guanosine monophosphate (cGMP) level through activation of the soluble guanylate cyclise[20] and subsequent activation of cGMP-dependent kinases in the responder cells.

The small quantities of NO formed during synaptic transmission modulate neuronal signalling, but excess NO mediates neurotoxicity. The NO/cGMP signal transduction pathways have been implicated in wide range of neuronal functions including modulation of neurotransmitter release. Several neurotransmitters such as acetylcholine, dopamine, nonepinephrine, neuroactive amino acids, and other classical neurotransmitters are suggested to be affected by NO in the brain. The effects of NO/cGMP on neuronal differentiation and survival suggest that NO/cGMP regulate gene expression in the nervous system[21,22] and have been linked in the regulation of hippocampal neurogenesis. Persistent neurogenesis occurs in the adult mammalian hippocampus throughout life, including humans,[23] and pathological amount of NO can suppress the normal adult mammalian neurogenesis.[24] Thus, depression may be associated with lack of hippocampal neurogenesis although it is a complex disorder that targets more than one region of the brain. Moreover, pathological amount of NO in the neurons lead to the generation of toxic reactive oxygen species and of toxic amounts of NO radicals,[25] thus damaging the neurons and giving rise to various affective disorders like MDD.

Objective of the study

The objective of the study was to determine the relationship between the pathophysiology of MDD and serum Mg^{++} and serum Ca^{++} levels.

Materials and methods

The study was carried out in the Department of Psychiatry, Gauhati Medical College Hospital (GMCH), Guwahati and biochemical tests were carried out in the Department of Biochemistry, GMCH. The duration of the study was of about 11 months, i.e. from January 2011 to November 2011. The study received the ethical approval from the institutional review board. Moreover, informed consent for participations in the study was obtained from the subjects/guardian of the patients after explaining to them the significance of the tests, the aims of the study, and the anticipated results. Further, as the study was a case-control study, samples were selected from two groups–case group and control group.

Case group

The case group consisted 30 patients with MDD from among the indoor and outdoor patients of the Department of Psychiatry of GMCH. And most importantly, they were in the state of depression for a period ranging from one to seven months and were identified by psychiatrist, GMCH as having MDD as per the fourth edition of DSM (DSM-IV) criteria.[26] Further, the subjects of the case group were selected over a period of ten months and efforts were made to select only one patient in a day. This was done to ensure that proper biochemical tests of blood sample can be carried out.

Control group

The subjects of the control group were selected randomly from a group of 90 individuals (60 females and 30 males). The group consisted of healthy individuals without any psychiatric diseases from different sections of the society and willing to co-operate voluntarily in this study. However, while selecting 30 subjects from the pool of 90, focus had been on selecting only 'age and sex matched' individuals (with respect to subjects of the case group).

Inclusion and exclusion criteria

The subjects–both male and female–should be between 15 to 64 years (both inclusive) and meet DSM-IV criteria for MDD. Further, they should be non-smokers and non-alcoholics. However, female patients during pregnancy and lactation were excluded. Also excluded were those who were alcohol/drug abuse or dependence (during the one year period prior to the study), those who had been taking medications for any medical reasons including but not limited to psychiatric

medications, and also those with any clinically significant abnormality evident in routine serum biochemistry.

Methods of evaluation

Biochemical analysis: Estimation of the parameters of the study–serum Mg^{++} and serum Ca^{++}–was done by using spectrophotometer (Spectra scan UV 2600). For this, fresh samples of blood were collected for the subjects of control as well as case groups.

Statistical analysis: Result values of serum Mg^{++} and serum Ca^{++} of subjects of case group (before treatment) were compared with that of subjects of control group by using Independent 't' test. SPSS 16.0 for Windows was used for data analysis.

Results and observations

Age and sex of subjects under control and case groups

The maximum number of subjects present in the case group as well in the control group was in the age class of 25 to 34 years with a relative frequency of 0.433 in both the groups. This was followed by the age class 15 to 24 years with a relative frequency of 0.300. On the contrary, the frequency was the lowest in the age class of 55 to 64 years in both the groups with a relative frequency of 0.033. Further, out of total number of subjects in control and case group, 21 were females (70%) and nine were males (30%).

Serum magnesium and serum calcium

The distribution of values of serum Mg^{++} and serum Ca^{++} of subjects in control and case (before treatment) groups as obtained from biochemical tests are shown in the tables below:

From the Table 1, it can be seen that the level of serum Mg^{++} among subjects of case group (before treatment) was lower than that of subjects of control group. On the other hand, Table 2 highlights that the level of serum Ca^{++} among subject of case group was relatively higher than that of subjects of control group.

Analysis of data reveals the mean value of serum Mg^{++} among subjects of control group was higher than that of the subjects of the case (before treatment) group. However, with $t=2.664$ and $p=0.0101$, and as $p<\alpha$ (=0.05), it can be inferred that there is a significant difference between the mean values of serum Mg^{++} among subjects of control and case (before treatment) groups (Table 3).

Similarly, analysis of data reveals the mean value of serum Ca^{++} among subjects of control group was less than that of the subjects of the case (before treatment) group. Further, with $t=2.075$ and $p=0.0434$, and as $p<\alpha$ (=0.05), it can be inferred that there is a significant difference between the mean values of serum Ca^{++} among subjects of control and case (before treatment) groups (Table 3).

Table 1: Frequency distribution of serum magnesium in control and case (before treatment) groups

Class interval	Control group		Case group (before treatment)	
	Male	Female	Male	Female
1.5 to 1.7 mg/dL	0	0	5	8
1.8 to 2.0 mg/dL	7	15	2	7
2.1 to 2.3 mg/dL	2	4	2	6
2.4 to 2.6 mg/dL	0	2	0	0
2.7 to 2.9 mg/dL	0	0	0	0
Total	9	21	9	21

Table 2: Frequency distribution of serum calcium in control and case (before treatment) groups

Class interval	Control group		Case group (before treatment)	
	Male	Female	Male	Female
8.4 to 8.9 mg/dL	0	2	1	2
9.0 to 9.5 mg/dL	1	5	1	3
9.6 to 10.1 mg/dL	5	10	3	5
10.2 to 10.7 mg/dL	3	4	2	7
10.8 to 11.3 mg/dL	0	0	2	4
Total	9	21	9	21

Discussion

Several studies have examined serum Mg^{++} and serum Ca^{++} in depression. With regard to Ca^{++}, there is a reasonable consensus among studies that serum Ca^{++} levels are increased in depression. However, data on serum Mg^{++} levels have been more inconsistent, and both increase and decrease have been observed in depressed patients.[4]

Mg^{++} ions regulate Ca^{++} ions flow in the neuronal NMDA channels, helping to regulate neuronal NO production. There can be excessive influx of extracellular Ca^{++} ions into the neuronal cells in case of low Mg^{++} ion concentration, because in case of Mg^{++} deficit, there is a failure of blockade of extra amount of Ca^{++} ions through the NMDA channels, which give rise to production of pathological amount of NO. The excess amount of NO, following its synthesis at the post-synaptic sites, may diffuse to the presynaptic terminals, giving rise to various pathological effects which may manifest as depression.

Mg^{++} intake has steadily declined over the preceding century, due to the changes in the dietary practices such as more intake of processed food items and complete removal of minerals from drinking water processed by distillation and reverse osmosis. Only 16% of the original Mg^{++} found in whole wheat remains in refined wheat processed foods.[27] As a result, there is a significant decrease in the average bioavailable Mg^{++} consumption, resulting in significant and unhealthy Mg^{++}-deficiency in the majority of the population in the present century.[28] Also dietary choices of high Ca^{++} diet prevent absorption of Mg^{++} in the intestinal tract, adversely affecting health.

Mg^{++} ions deficit may also be induced by stress hormones.[27] This decline in Mg^{++} caused by excessive stress hormones is mainly seen in chronic stress which can, in due course, manifest as depression. Also people

Table 3: Statistical comparison of serum magnesium and serum calcium among subjects of control and case (before treatment) groups

Statistics	Serum magnesium		Serum calcium	
	Control group	Case group (before treatment)	Control group	Case group (before treatment)
Mean	1.9967	1.8633	9.7633	10.080
Standard deviation	±0.16914	±0.21573	±0.44682	±0.70669
t-value	2.664		2.075	
p-value	0.0101		0.0434	

tend to increase the dietary intake of Ca^{++} to meet the stress, causing further Mg^{++} deficit. Low Ca^{++} and high Mg^{++} (1:2) ratio in diet may be vastly beneficial to overall health, including depression and cardiovascular diseases than the previously thought of the beneficial effect of a high Ca^{++} and low Mg^{++} (2:1) diet.[29] Oral Mg^{++} treatment was described as being effective in treating major depression while restricting excess dietary Ca^{++}. In addition, it was found that supplementing antidepressant drugs with Mg^{++} significantly reduced the effective doses of these drugs.[30]

Apart from dietary factors, analysis of the parathyroid hormone (PTH) status can be done in patients with depression, because hyperparathyroidism is a leading cause of elevated Ca^{++} level in patients presenting in primary care setting. The patients with elevated PTH often present with non-specific symptoms including mood disturbances. Also hypercalcaemia and hypercalcuria decreases renal Mg^{++} reabsorption and so Mg^{++} deficiency is frequently present in hypercalcaemic states like hyperparathyroidism.[31]

Conclusion

The present study has found that serum Mg^{++} level decreases in patient who are depressive when compared to the healthy controls. Also it was found that serum Ca^{++} increases in depression. Thus, conclusively it can be said that alterations in the concentrations of Mg^{++} and Ca^{++} may play a role in depressive illnesses. The result of the present study can be only seen as very preliminary due to low sample size and should be confirmed by larger studies. It is, however, clear from the study that some alterations in the concentrations of Mg^{++} and Ca^{++} in the human body may play a possible role in causing various mood disorders like MDD.

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