Serum Calcium and Magnesium Levels do not correlate with Severity of Major Depressive Disorder

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Abstract

Major Depressive Disorder (MDD) is one of the leading cause of morbidity amongst psychiatric illness. Pathophysiology of MDD is still a matter of research and not much is known about it. Although, it is certain that neurotransmitters are implicated in MDD, yet there are no investigations available which can confirm this and hence help in establishing the diagnosis. Last century has much debated about these neurotransmitters' and elements which play a role in their release in synapse. Sodium, Potassium, Calcium, Magnesium, Zinc are a few elements which are involved in physiology of neurons and therefore various hypothesis have been put forward regarding these elements and their role in treatment of MDD. This study made an attempt to review correlation between serum levels of Sodium, Potassium, Calcium, Magnesium and severity of MDD using PHQ-9 (Patient Health Questionnaire - 9) scale. A total of 119 patients were diagnosed with MDD (over a period of 4 months) out of which 79 patients were included after applying inclusion and exclusion criteria. PHQ-9 categorized patients in no depression (n = 7), minimal (n = 11), mild (n = 34), moderately severe (n = 20) and severe (n = 7).Mean level of serum Sodium, Potassium, Calcium, Magnesium were found to be 139 ± 4.101 mEq/L, 4.05 ± 0.439mEq/L, 9.1 ± 0.49 mg/dl, 1.85 ± 0.311 mg/dl respectively. Fifty four out of 79 patients diagnosed with major depressive episode in our sample had no abnormality in serum levels of any electrolyte, while seven had abnormality in 2 or more electrolyte levels. Data was analyzed and there seemed to be no evident correlation between serum levels of Sodium, Potassium, Calcium, Magnesium with severity of MDD. In our study with patients of MDD we found no correlation in severity of depressive symptoms with serum electrolyte levels of Sodium, Potassium, Calcium, Magnesium.

Key Words: Calcium, Major depressive disorder, Magnesium**,** PHQ-9

Introduction

Major Depressive Disorder, MDD, is a common psychiatric condition which affects at least one in four individual during his/ her lifetime.[1] MDD is characterized by low mood and/ or irritability with anhedonia and decreased energy and easy fatigability associated with other symptoms like depressive cognition, biological dysfunction, somatic symptoms and in few proportion of cases delusions and hallucinations.[2] Various psychological and biological theories have been postulated for etiology of depressive symptoms with recent literature focusing heavily on neurobiological & biological basis of depression.[3]

Variations in electrolyte levels in blood, platelets, erythrocytes, cerebrospinal fluid have been noted in many mental illnesses. Among anxiety disorders, no significant changes in levels of calcium and magnesium have been noted in generalized anxiety disorders[4] and panic disorder[5] while elevated calcium and decreased magnesium are noted in obsessive compulsive disorder.[6] Among psychotic disorders, in idiopathic hypoparathyroidism associated psychosis, high dose antipsychotic medications were found to be less helpful unless serum calcium and magnesium levels were corrected.[7] In schizophrenia patients with suicidal attempt, higher concentration of platelet magnesium with low serum calcium has been noted.[8] Interestingly calcium levels have been reported to increase prior to onset of catatonic stupor in schizophrenia.[9]

Electrolyte dysfunction has been reported with depressive disorders since last six decades.[10] These include not only the macro elements like sodium, potassium, magnesium, calcium and phosphates but also micro elements like Zinc, iron, copper and manganese.[5]Calcium and magnesium are the most predominant intracellular cation.[11]Calcium and

magnesium levels in depression have shown mixed results with certain studies reporting increased levels while others showing reduction in levels.[5]It has also been postulated that depression may be associated with changes in sodium levels based on the role of argenine vasopressin in contributing to Hypothlamic pituitary axis (HPA) dysfunction in MDD. Lower plasma potassium levels have been reported in treatment naïve depressed patients[12]

The objective of the study is to assess serum levels of sodium, potassium, calcium and magnesium and correlate with severity of depression in treatment naïve patients.

Methodology

This is a cross-sectional study of patients seeking treatment for major depressive disorder, presenting at a rural tertiary care centre in north India. The inclusion criteria were (a) diagnosis of major depressive episode as per DSM-V criteria, (b) of either male or female gender, (c) age >18 years, (d) availability of informant and (e) informed consent. Exclusion criteria include (a) any major medical, surgical, psychiatric disorder including mental retardation and drug dependence (except nicotine), (b) patient with anemia, (c) patients taking psychotropics for last 6 weeks, and (d) pregnancy.

All patients fulfilling the criteria were encouraged to participate in the study. Psychiatric disorders, other than MDD, were excluded by clinical interview and history by one of the authors (ARR). Medical screening was done by clinical examination and investigations such as complete blood count, renal function test, liver function test and blood sugar. After obtaining informed consent, severity of depressive episode was assessed using the Patient Health Questionnaire-9. PHQ-9 is a multipurpose instrument that is used for screening, diagnosis, monitoring and measuring the severity of depression. Based on PHQ-9 scores, severity of depressive episode can be categorized as no depression (0-4), minimal (5-9), mild (10-14), moderate-severe (15-19) and severe (≥20).[13] The Hindi version of this instrument is freely available.[13]In addition, blood sample was drawn for assessment of serum levels of sodium, potassium, calcium and magnesium. Investigations were done using fully automatic Chemistry Analysis, EVO 800 (Roche Diagnostics). Quantitative assessment of electrolytes was done using standard reagents; serum magnesium was estimated by Xilydyl Blue method and serum calcium was evaluated by Arsenazo III method.

Ethical committee approved the study. Informed consent was obtained from the study participants. All the questionnaires were manually checked and edited for completeness and were then coded for computer entry. After compilation of collected data, analysis was done using Statistical Package for Social Sciences (SPSS), version 20 (IBM, Chicago, USA). The results were expressed using appropriate statistical methods like mean, standard deviation etc. Correlation analysis (Spearman's rho) was performed to find out correlation if any in severity of depressive symptoms with serum electrolyte levels.

Results

A total of 119 patients were diagnosed with MDD during the study period of Feb to May 2015. Forty patients were excluded for anemia (n=5), comorbid medical/ surgical disorder (n=7), comorbid psychiatric disorder including drug use and mental retardation (n=26) and pregnancy (n=2). Seventy nine patients (36 male, 43 female) fulfilled the study criteria.

Majority of the patients were uneducated (n=54, 68.3%), married (n=64, 81%) and belonging to low socio-economic status (n=66, 83.5%). Average age of patients was 34.21 (±13.28) years. Serum levels of sodium, potassium, calcium and magnesium with depression scores on PHQ-9 are shown in table 1 and correlation of level of serum electrolytes with depression scores is given in table 2. Magnesium correlated negatively with severity of depression (8%) whereas calcium showed little positive correlation (10%) with depression both of which were not observed to be statistically significant (significance level 0.54 and 0.45 respectively). Combined effect of calcium and magnesium correlated well (34%) with severity of depression. As can be observed there is no correlation of serum levels of any electrolyte with depression scores.

Table 1: Serum electrolyte levels in patients

PHQ-9 Score		Serum Sodium (mEq/L)	Serum Potassium (mEq/L)	Serum Calcium (mg/dl)	Serum Magnesium (mg/dl)
0-4 (Nil) N = 7	Mean ± SD	139.036 ± 4.278	4.05 ± 0.438	9.092 ± 0.494	1.836 ± 0.340
5-9 (Minimal) N = 11	Mean ± SD	140 ± 4.22	4.1 ± 0.44	9.095 ± 0.479	1.848 ± 0.322
10-14 (Mild) N = 34	Mean ± SD	139 ± 4.07	4 ± 0.43	9.15 ± 0.495	1.85 ± 0.311
15-19 (Moderately severe) N = 20	Mean ± SD	139 ± 4.17	4 ± 0.43	9.11 ± 0.482	1.853 ± 0.317
>20 (Severe) N = 7	Mean ± SD	139 ± 4.04	4 ± 0.44	9.146 ± 0.496	1.854 ± 0.315

Table 2: Correlation of calium and magnesium levels with severity of depression

			MG	CA	PHQ-9 Scoring
Spearman's rho	MG	Correlation Coefficient	1.000	.344**	-.082
		Sig. (2-tailed)	.	.008	.543
	CA	Correlation Coefficient	.344**	1.000	.101
		Sig. (2-tailed)	.008	.	.456
	PHQ-9 Scoring	Correlation Coefficient	-.082	.101	1.000
		Sig. (2-tailed)	.543	.456	.

Discussion

Neurotransmitter model of pathophysiology of depression does implicate Sodium, Potassium, Magnes-ium and Calcium levels to a certain extent, where imbalance of these cations result in disturbance of ionic potential leading to low level of neurotransm-itters (serotonin, norepinephrine, dopamine) resulting in subsequent depression.[14]In this cross sectional study we have assessed the serum electrolytes levels of sodium, potassium, calcium and magnesium in treatment naïve patients with major depressive disorder and correlated with severity of depressive episode.

Fifty four out of 79 patients diagnosed with major depressive episode in our sample had no abnormality in serum levels of any electrolyte. Eighteen patients had at least one electrolyte abnormality while seven had abnormality in 2 or more electrolyte levels. Distribution of abnormal electrolyte levels is: hyponatremia (n=10, 12.7%), hypernatremia (n=2, 2.5%), hypokalemia (n=5, 6.3%), hyperkalemia (n=4, 5.1%), hypocalcemia (n=6, 7.6%), hypercalcemia (n=2, 2.5%) and hypomagne-semia (n=6, 7.6%).

This study did not found any deviation from the normal in respect to Magnesium and Calcium level in stratified groups of depressed patients, classified with the help of PHQ-9. In a similar study, serum levels of calcium and magnesium in 105 middle-aged women with depression did not correlate with severity of depression scored on Zung self-rating depression scale.[15]Widmer et al., (1995), have reported increased magnesium in plasma as well as erythrocytes of moderate and severely depressed patients.[16,12] They postulated that since hypomagnaesemia is associated with

hyperexcitability, hypermagnaesemia might be associated with psychomotor retardation seen in depression.[16] However, recent studies have observed hypomagnesemia in patients with depression with increase in calcium magnesium ratio.[17,18,19,20] Indeed, Eby et al., 2010, based on their review, have suggested that there is sufficient evidence to implicate dietary magnesium deficiency as cause of treatment resistancein MDD depression.[18] A large study involving nearly 13000 Spanish university students observed over a median period of 6.3 years however, concluded that no inverse association of magnesium intake and depressive disorder could be established.[11]

Magnesium is involved in hundreds of intracellular enzymatic reactions .[21] In neurons, it acts as calcium antagonist and is voltage dependent blocker of N-Methyl-D-aspartate receptor.[21] Irrespective of the inconclusive correlation of findings, magnesium has been promoted for use treatment of depression as a synergistic drug. Theoretical hypothesis of inhibition of hippocampal kindling by blocking NMDA receptors using Magnesium have been put forward as a rationale for use of magnesium in depression. Magnesium levels in CSF have indeed been found low in patients with treatment resistant MDD and those who have attempted suicide.[18]Magnesium preparations have been found to be effective agents for migraine, pre-eclampsia, arrhythmias, premenstrual tension and are frequently used in homeopathic system of medicine.[22]

Similarly, with regard to calcium, studies have shown hypocalcemia[18], hypercalcemia[15,23] and normal serum calcium levels[12]in those with major depressive disorder. In a study by Linder et al., 1989, diurnal serum calcium levels were correlated with the severity of depression using the comprehensive psychopath-ology rating scale. The authors found that depressive symptoms correlated negatively with morning plasma levels in acute stage and positively in remission and long standing depression.[23]It has also been reported that urinary excretion of calcium may fail to increase in summer months in those with bipolar disorder as compared to control subjects .[24]With regard to use of Calcium supplementation in depression, it has been reportedly precipitated or worsen agitation in thosewith bipolar disorders .[25]

Few studies have reported variations in plasma concentration of either sodium or potassium in depressed patients. Frazer et al (1983) and Widmer J et al (1995) showed a small increase in Na+ in major depression patients.[26,16] Ozdemir et al., postulates the role of hypernatremia in depression based on that observations that treatment modalities like selective serotonin receptor inhibitors and electroconvulsive therapy tend to cause hyponatremia.[27] He further postulates the role of argentine vasopressin in hypothalamo pituitary axis (HPA) dysfunction in depression which can cause hypernatremia.[27] In this study however, sodium and potassium levels were found to be normal in all subgroups of depression.

One of the limitation of the study is that serum levels of electrolytes do not necessarily correlate with their levels in brain. Phosphorus magnetic resonance spectroscopy seems to be currently the best tool for in vivo assessing magnesium level in the human brain (17).[28] Thus more advanced research methods are required to establish importance of Magnesium and Calcium imbalance in depressed patients. As such this study refute any positive or negative correlation of Magnesium and Calcium blood levels amongst depressed patients, it also showed magnesium and calcium levels were equivocal in different grades (minimal, mild, moderate, severe) of depression.

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