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A COMPARATIVE STUDY FOR ASSESSMENT OF SERUM SEROTONIN & MAGNESIUM CONCENTRATION BETWEEN NEWLY DIAGNOSED MENTALLY DEPRESSED PATIENTS & HEALTHY VOLUNTEERS IN A TERTIARY CARE HOSPITAL IN EASTERN INDIA

Biochemistry

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ABSTRACT

Pathophysiology of many psychiatric disorders like major depression involves monoamine transmitters like serotonin & substances that reduces NMDA function,including the magnesium modulated, mono aminergic pathway. Worldwide study showed decreased level of serum serotonin & magnesium in acute depressed patients. This case control,non interventional,institutional study was carried out in Dept. Of Biochemistry of Medical College & Hospital, Kolkata between June 2019 to August 2019, in 50 acute depressed recently diagnosed patients & 50 age and sex matched mentally & physically healthy controls.In the depressed group mean serum serotonin level (139 +- 41 ng/ml) was significantly lower than healthy controls (230 +- 25 ng/ml). So was the mean serum magnesium level which was also significantly lower in depressed group (1.1 +- 0.08 mg/dl) than healthy controls (2.1+-0.17 mg/dl). This result was in agreement with most of the researches done worldwide.

KEYWORDS

Serotonin , Magnesium , Depression.

INTRODUCTION :-

Magnesium (Mg) plays very important role of cofactor for many enzymatic reactions, such as energy production, active ion transport across cell membranes , synthesis of essential biomolecules, cell signalling and cell migration [1]. It is also an essential cofactor for the activation of tryptophan hydrolase [2], it is also present in human platelets for binding of serotonin to its receptor [3,4]. It has been proved that at physiological concentrations, Mg blocks N-methyl- D-aspartate (NMDA) receptors in neurons [5], modulates GABA ergic neurotransmission, and affects numerous transduction pathways [6, 7].

On the other hand, Major depression, one of the affective disorders, is a mood disorder characterized by a variety of symptoms which include sense of inadequacy, despondency, decreased activity, pessimism, anhedonia and sadness and these symptoms severely disrupt and adversely affect the person's life, and sometimes suicide is attempted . Irritability, insomnia, lethargy, agitation and anxiety often accompany depression. The World Health Organization showed that unipolar major depression was the leading cause of disability globally in 1990, and suggests that depression and heart disease will be the most common diseases on Earth by 2020 [8], with both of these diseases having strong magnesium deficiency components.

There are also several researches showing clinical evidence implicating alterations of the serotonergic system in the etiology of major depressive disorders. A general serotonin vulnerability has been proposed as a major risk factor in depression, consisting of many risk factors from different components of 5-HT action like synthesis,transport & metabolism. The effects of abnormal 5-HT synthesis, receptor function and genetic polymorphisms are considered as major risk factors for depression[9].

Several studies have demonstrated antidepressant and anti-anxiety-like effects of Mg in animal models [10-12] while an Mg-deficient diet increased depression and anxiety-related behaviour in mice [13,14]. Epidemiological studies have demonstrated an inverse relationship between magnesium intake and depressive symptoms in community-dwelling,middle-aged and older adults [15].

So, in a nutshell, pathophysiology and treatment of depression involves monoamine neurotransmitters like serotonin and substances that reduce NMDA function, including the magnesium modulated, monoaminergic pathway [16]. There is a shortage of research in this field in Eastern India. Therefore, the objective of the present study is to estimate serum levels of serotonin and magnesium in newly diagnosed depressed patients, (who are still not exposed to any kind of anti depressant or anti psychotic medication) & healthy volunteers in a Tertiary care hospital in Eastern India & to compare the levels to see whether there is any difference or not.

MATERIALS & METHODS :

The present study was carried out in the Department of Biochemistry of Medical College and Hospital, Kolkata from June 2019 to August 2019. This case control study was conducted in a study population comprising of 100 subjects with age ranging from 27 to 70 years who sought mental health care in the psychiatric medicine outpatient departments in Medical College and hospital,Kolkata and also the age and sex matched healthy patient parties & male & female technicians & healthy volunteers. Of these 100 subjects, 50 were recently diagnosed depressed patients and 50 were mentally & physically healthy men & women.

EXCLUSION CRITERIA:

Diagnosed patients of depression and/or other psychiatric disorders (diagnosed by psychiatric department by thorough questioning & history taking), patients taking wide variety of drugs that include monoamine oxidase (MAO) inhibitors, tricyclic compounds, selective serotonin reuptake inhibitors (SSRIs), and lithium (for bipolar disorder) were excluded as these are known factors to alter the serum serotonin level.

Patients suffering from malnutrition were excluded as it is a known causative factor for decreased magnesium level. Low magnesium level in the body may also occur due to defects in its absorption or as a result of its renal loss (for example in case of renal failure, diabetes, alcoholism, treatment with antidiuretics, aminoglycosides, fluoroquinolones, cisplatin, digoxin, cyclosporine, amphotericin B) [17] etc. , so patients suffering from diabetes and/or any other life threatening disease, having history of alcoholism,obese patients,pregnant & lactating females & patients taking the above mentioned medications were excluded from the study.

The presence or absence of depression and /or presence of any other psychiatric disorder were diagnosed by following method : Initial psychiatric interviews were conducted in the psychiatric OPD. The evaluation consisted of reviewing the history, data on current and previous medications, and alcohol intake. This was followed by a semi-structured interview, with the purpose of establishing the ICD-10 (International Classification of Diseases and Related Health Problems, Tenth Revision, 2004) criteria for diagnosis of F32.2 and F33.2, with or without intentional self harm (X60-X84) .

After the diagnosis of depression was made , only the newly diagnosed patients having no exposure to any kind of anti depressant or anti psychotic medications were chosen. Taking all aseptic and antiseptic precautions, 5ml of blood was drawn from the median cubital vein. Fasting samples were used for all the investigations. Separated serum was used and tests were done within eight hours of collection, or else the samples were preserved at -20ºC for future use.

Estimation of serum magnesium was done by Xylidyl-blue

method[18] by sclavo diagnostics, Xylidyl-blue forms a soluble coloured compound with magnesium in an alkaline ambient, with a maximum absorbance between 510 and 520 nm. The intensity of the colour of the Mg-xylidyl-blue compound is directly correlated to the magnesium concentration in the sample. The estimation was done in konelab 6000 i prime autoanalyser.
Serotonin was assayed by competitive ELISA method by LDN immunoassays & services kit[19].

RESULTS :
The control group comprised of 50 healthy male & female having no psychiatric complaints or symptoms (age group 27 – 70 years), and case group comprised of 50 patients who are newly diagnosed depressed patients (age group 27-70 years), both were chosen keeping in mind the inclusion- exclusion criteria. The data was analysed by SPSS recent version software, normality was determined by kolmogorov-smirnov goodness- of- fit test.

Comparison was done between case and control group.
The case group,which comprises the newly diagnosed depressed patients- their mean serotonin level was -> 139+- 41 ng/ml, which was significantly lower than the normal control group -> 230+- 25 ng/ml.

The magnesium level in case group was -> 1.1+- 0.08 mg/dl, which was significantly lower than control group -> 2.1+- 0.17 mg/dl.

DISCUSSION :
Magnesium ,is known to be involved in proper functioning of cardiovascular, alimentary, endocrine and osteoarticular systems. An adult contains about 24 grams of magnesium, of which more than 50 percent is localized in bones while the rest is found in soft tissues and plasma/serum [20]. According to literature [21] magnesium is widely connected with brain biochemistry as well as the fluidity of neuronal membrane. Thus, a variety of neuromuscular and psychiatric symptoms (i.e., hyperexcitability, agitation, tetany, headaches, seizures, ataxia, vertigo, muscular weakness, tremors, irritability, anxiety, insomnia, nervous fits, lipothymias, fatigue, confusion, hallucinations, depression) was observed in magnesium deficiency. All of them were reversible by restoration of normal brain magnesium level [22].Experimentally induced magnesium deficiency resulted in depressionlike behavior in rodents ,which was effectively managed by antidepressants[23,24].

There are several reports on higher concentration of magnesium in depressed patients [25,26,27] and more than a few on the lower magnesium level [28,29,30,31]; some authors claim that there is no difference in the serum/plasma concentrations of magnesium ion or calcium/magnesium ratios between the affected subjects and the control group [32,33].

George A. Eby et al showed that magnesium ion involvement in nerve cell electrical conduction activity is in a regulatory fashion with calcium ions. Magnesium ions normally block calcium ions within the N-methyl-D-aspartate (NMDA) receptor channel. When magnesium ions are missing, the channel is unblocked and calcium ions and sodium ions enter the postsynaptic neuron as potassium exits. Sapolsky et al [34] suggested the same by showing that magnesium depletion was likely to be deleterious to neurons possibly by causing NMDA-coupled calcium channels to be biased towards opening. Paul [35] suggested that any means of reducing pathological neuronal calcium ion flow to reduce resulting pathological nitric oxide neuronal output would have antidepressant effects, they also reported that magnesium deficiency increased nitric oxide production by increasing calcium ion entry. Too much calcium ion and glutamate with insufficient magnesium ion, particularly in the hippocampus, plays a vital role in brain cell synaptic dysfunction leading to depression and other mood and behavioral disorders.

Magnesium has the property to suppress hippocampal kindling by following mechanisms,it reduces the release of adrenocorticotrophic hormone (ACTH) and to affect adrenocortical sensitivity to ACTH. The role of magnesium in the central nervous system could be mediated via the N-methyl-D-aspartate-antagonistic, g-aminobutyric acid A-agonistic or the angiotensin II-antagonistic property of this ion.

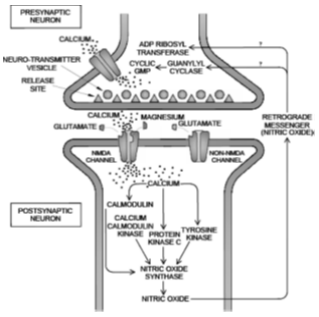

Figure 1 Magnesium has a role in regulating calcium ion flow in neurons.

A direct impact of magnesium on the function of the transport protein p-glycoprotein at the level of the blood-brain barrier has also been demonstrated, possibly influencing the access of corticosteroids to the brain. Furthermore, magnesium dampens the calcium ion-protein kinase C related neurotransmission and stimulates the Na–K-ATPase. All these systems have been reported to be involved in the pathophysiology of depression.

Banki et al. [36] showed that both cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA) and magnesium ions are low in suicidal depressives. Levine et al. [37] showed that there were high serum and cerebrospinal fluid calcium to magnesium ratios in recently hospitalized acutely depressed patients. Kalinin et al. [38] used magnesium lactate and vitamin B-6 as treatment, (required for absorption of magnesium) showed benefit in anxiety and depression treatment in patients with epilepsy.

Hypothyroidism, a known cause of depression, is associated with low magnesium with circulating T4 levels being directly correlated with magnesium serum levels [39]. The depression attributable to hypothyroidism is hypothesized to be caused by resultant low magnesium, which is restored to normal only by proper treatment of hypothyroidism. Postpartum depression can be much more severe than clinical depression. The fetus and placenta absorb enormous amounts of nutrients (especially magnesium) from the mother and loss of magnesium to the fetus coupled with insufficient intake of magnesium by the mother is hypothesized to be the cause of postpartum depression. Lactation is also known to deplete maternal magnesium [40].

Wacker WE et al also described that low calcium and high magnesium (1:2 ratio) intake is vastly more beneficial to overall health, including depression, cardiovascular disease and osteoporosis than high calcium and low magnesium (2:1 ratio). Excessive calcium intake prevents absorption of magnesium in the intestinal tract, adversely affecting mental health, making people prone to depression.[40].

Serotonin is one of the most powerful neurotransmitters, with widespread effects. Psychiatric
disorders including depression, anxiety, aggression, compulsive behavior, substance abuse, bulimia, seasonal affective disorder, childhood hyperactivity, mania, hyper sexuality, schizophrenia, and behavioral disorders have been associated with impaired central serotonin function.

Serotonin (5- HT; 5-hydroxytryptamine) occurs naturally in the body. In the periphery, serotonin acts both as a gastrointestinal regulating agent and a modulator of blood vessel tone. Only 2% of the body's serotonin is found in the brain as a neurotransmitter .As a neurotransmitter, serotonin is involved in the modulation of motor function, pain perception, appetite and outflow from the sympathetic nervous system .

5-HT hypothesis of major depression has beenformulated in three distinct ways. First a deficit in serotonergic activity is a proximate cause of depression. Second a deficit in serotonergic activity is important as a vulnerability factor in major depression. Third, (now of historical interest only) increased vulnerability to major depression to enhanced serotonergic activity. Most new (as well as older) antidepressants inhibit the re-uptake of serotonin from the synapse and alter 5-HTt protein and mRNA levels.

Studies have shown that free serotonin is raised in stressed mammals and severely ill humans. The same parameter is normal or slightly lowered in dysthymic and endogenous depressed humans. Low CSF concentration of 5 HIAA has been associated with higher lifetime aggressiveness, impulsiveness and greater suicidal intent in patients with major depressive disorders [41].

K Sarai et al [42] found out the following facts about the relationship between serotonin and depression after studying depressed patients before and after treatment- the serum levels and diurnal rhythm of serotonin before and during treatment were investigated in 65 manic –depressive patients, comparing with those in 34 normal controls and 13 schizophrenics.

a) The serum serotonin level in 40 newly admitted depressive patients who had not been medicated (127±58 ng/ml) was significantly lower than that in normal controls (221±96ng/ml), b) The serum serotonin level in 24 recovering patients with depression had the tendency to return to normal while under treatment with imipramine type antidepressants (281±189 ng/ml), c) The serum serotonin level in 10 manic patients (365±85 ng/ml) was significantly higher than that in normal controls, d) After the injection of imipramine to depressive patients, serum serotonin level tended to increase (1.5 times). e) Electroconvulsive shock did not appear to alter the serum serotonin level in depressive patients and normal dogs, f) As for the diurnal rhythm of serum serotonin of depressive patients, the serotonin level in the morning was the lowest, which seemed to be related to the worst depressed mood in the morning. In the manic patients, the serotonin level at 20.00 hours was the highest. This pattern of rhythm resembled that of normal controls.

According to a study by Mann J et al (1989) [43], the greatest reduction in CSF 5-HIAA is associated with unipolar depression and absent in bipolar disorder.

Five of seven studies have reported a decrease in 5-HT or 5-HIAA levels within the brain of suicide victims or suicide attempters. The reduced levels were found localized to the brainstem with only one study reporting reductions in higher cortical centers.

The role of serotonin in affective illness is based in part on the following pathophysiological changes found in depression : I) decreased brainstem 5-HT and / or 5-HIAA, 2) increased plasma tryptophan clearance, 3) that reduction in tryptophan induces depressive episodes in the depressed , 4) t hat serotonin uptake sites downregulate while some classes of serotonin receptors up-regulate, 5) that neuroendocrine activity is subresponsive to serotonin stimulation and 6) that many effective antidepressant therapies increase serotoninergic activity . [44,45,46].

So, the findings of our study is in agreement with most of the studies done worldwide, in this study done in Eastern Indian population,we also found lower amount of serotonin & magnesium in acute , recently diagnosed depressed patients than age and sex matched physically & mentally fit control group.

But the limitation of this study was small sample size & there was no repeat testing done after anti depressant & anti psychotic medication.

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