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STUDY OF PLASMA HOMOCYSTEINE LEVELS IN PATIENTS OF DEPRESSION AND SCHIZOPHRENIA

Biochemistry

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ABSTRACT

Introduction: Homocysteine (Hcy) has gained recognition as a marker of atherosclerosis and resulting vascular disease. Its role in psychiatric disorders has not been explored much.

Aims & Objectives: The present study was planned to assess the serum homocysteine levels in patients suffering from depression and schizophrenia and to explore the association of increased homocysteine levels with these psychiatric disorders.

Material & Method: Fifty patients diagnosed for depression and schizophrenia based on International Classification of diseases (ICD-10) were enrolled for the study. Fifty age and sex matched healthy individuals constituted the control group. Serum homocysteine levels were estimated for all enrolled subjects. Results obtained were compared statistically among the diseased and healthy control subjects.

Result: Mean serum homocysteine levels were significantly higher in the depression (P = 0.000) and schizophrenia (P = 0.003) patients. Further, a significant number of depression patients (42%) and schizophrenia patients were observed to have hyperhomocysteinemia.

Conclusion: Elevated Hcy concentration can be the underlying cause of psychiatric manifestations either directly or secondary to other biochemical derangements. The study suggests a strong association of hyperhomocysteinemia with psychiatric disorders specially depression. Screening of patients with depression or schizophrenia is therefore, strongly recommended.

KEYWORDS

depression, schizophrenia, homocysteine, hyperhomocysteinemia, psychiatric disorders

INTRODUCTION

Homocysteine (Hcy) is an amino acid which is a homolog of the amino acid cysteine, it differs only by having an additional methylene (-CH2-) group. Methionine is converted into S- Adenosylmethionine (SAM) which produces S-Adenosyl Homocysteine (SAH). Further SAH is converted or metabolized to Hcy. It can either undergo remethylation to form methionine or transulfuration to form Cysteine. Being an intermediate, Hcy levels are normally below 15 µmol/L.

Hyperhomocysteinemia has been identified as an independent risk factor for various diseases[1]. Moderately elevated Hcy concentrations are related to diseases such as renal and thyroid dysfunction, cancer, psoriasis, and diabetes as well as various drugs, alcohol, tobacco, coffee, older age and menopause[2]. Nowadays hyperhomocysteinemia has gained recognition as an independent risk factor for peripheral vascular, cardiovascular, and coronary artery disease (CAD). Elevated Hcy levels are found in almost one-third of all patients with atherosclerosis. Increase in the levels 12% above the upper limit of normal is associated with a threefold increase in the risk of acute myocardial infarction[3]. Its raised levels are also suggested to be correlated with the psychiatric disorders[4].

Schizophrenia and depression are common psychiatric disorders with an increasing incidence across the globe. With the increment in the number of patients suffering from these disorders, need for the understanding in terms of clinical as well as biochemical aspects becomes very much important. Various psychological, social, environmental, developmental, genetic, anatomical, biochemical and other factors are involved in etiology of schizophrenia and depression.

Depression is a major cause of morbidity worldwide and the proportion of the global population with depression is increasing rapidly. Schizophrenia is also ranked among the top 25 leading causes of disability worldwide[5]. The role of hyperhomocysteinemia in development of psychiatric disorders has not been explored much. Modern lifestyle influences the physical and mental behaviors of an individual. Though manifested as behavioural changes, psychiatric disorders like schizophrenia and depression may occur due to simple deficiency of nutrients or may be manifested due to certain biochemical derangements. The present study was therefore planned to study the plasma Hcy levels in patients of schizophrenia and depression.

MATERIALS AND METHODS

Based on the International Classification of Diseases (ICD 10) criteria, patients diagnosed for schizophrenia and depression (n=50 each), visiting the Out Patient Department (OPD) of Department of Psychiatry, Mahatma Gandhi Medical College & Hospital, Jaipur were enrolled for the study. 50 age and sex matched healthy subjects (n = 50) constituted the control group. The study was conducted after seeking approval from the **Institutional Ethics Committee (IEC)**. Patients above 65 years of age, with history of any chronic illness or any substance abuse were excluded from the study. Pediatric patients (below 18 years) and pregnant or lactating females were also not included in the study.

Blood samples were collected by venipuncture using standard aseptic technique. Plasma Hcys levels were estimated on VITROS 5600 Chemistry analyzer using Ortho Clinical diagnostics reagents. Results obtained were presented as mean + SD and compared statistically in the disease and control groups.

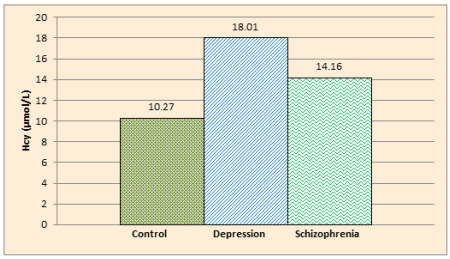
RESULT

Results obtained among the three group i.e. schizophrenia patients (n=50); depression patients (n=50), control group (n=50) were presented as mean ±SD and subjected to statistical evaluation using SPSS software. The results of patients groups were compared with those of control group by applying student's t-test (Table 1).

Mean age of the control and patients' groups was comparable. Mean value of Hcy in Schizophrenia patients group was 14.16± 8.40 µmol/L as compared to control group mean value i.e. 10.27 ± 3.28 µmol/L (P = 0.003). Serum Hcys levels were observed to be significantly higher in the Depression patient group also (P = 0.000). The mean Plasma Hcys level for depression patients was 18.01±12.47 µmol/L (Table 1; Figure 1).

Table 1: Distribution of age and sr. Hcy levels in between control and depression and schizophrenia patients

	Control (A)	Depression (B)	Schizophrenia (C)	A v/s B (P- value)	A v/s C (P- value)
Number of subjects (n)	50	50	50		
Age (years)	40.32 ± 10.86	36.94 ± 15.13	37.44 ± 9.88	NS	NS
Plasma Hcy (µmol/L)	10.27± 3.28	18.01±12.47	14.16±8.40	0.00	0.003



Hcys concentration > 15 µmol/L is considered as abnormal and the condition is termed as Hyperhomocysteinemia. Among the control group patients only 2 out of 50 i.e. 4% had Plasma Hcys > 15 µmol/L. On the contrary, among depression group, 42 % patients had Plasma Hcys concentration > 15 µmol/L (Table 2). On applying Chi-square test, a significant influence of the disease on Hcys levels was confirmed. Similarly, 30% of the Schizophrenic patients were found to have hyperhomocysteinemia (Table 3).

Table 2: Distribution of subjects on the basis of hyperhomocy steinemia in Control and Depression group

	Hcy <15.0 (µmol/L)	Hcy ≥15.0 (µmol/L)	Chi square (X^2)	P-value
Control	48 (96%)	2 (4%)	38.650	0.00
Depression	29 (58%)	21 (42%)		

Table 2.1: Distribution of subjects on the basis of hyperhomocy steinemia in Control and Schizophrenia group

	Hcy <15.0 (µmol/L)	Hcy ≥15.0 (µmol/L)	Chi square (X^2)	P-value
Control	48 (96%)	2 (4%)	22.147	0.00
Schizophrenia	35 (70%)	15 (30%)		

DISCUSSION

The present study was conducted to explore the importance of plasma Hcy levels in patients of schizophrenia and depression. Findings of the present study suggest that hyperhomocysteinemia can be associated with occurrence of Psychiatric disorders viz. Depression and Schizophrenia.

According to researches and published literature, major cause of increased serum levels of homocysteine include methionine loading; dietary deficiency of vitamin B12, folic acid and vitamin B66. It is so because the above mentioned vitamins are actively involved in utilization of homocysteine which is itself formed as an intermediate during conversion of methionine to cysteine. Other causes of hyperhomocysteinemia include renal disease[7] and genetic variation of the enzymes (such as methyl-tetrahydro- folate reductase *[MTHFR]* and cystathionine beta-synthatase *[CBS]*) essential for the metabolism of homocysteine. Any other factor that interferes with the absorption of nutrients like: inflammatory bowel disease, regular use of laxative or gastric atrophy can lead to higher homocysteine levels in blood[8, 9, 10]. Elevated homocysteine concentrations are also reported in persons on anticonvulsants and diuretics[11].

Schizophrenia is regarded as a chronic mental disorder which can be caused due to a combination of genetic and environmental factors like the living environment, drug use & prenatal stressors etc[12]. Increased Hcy levels have been found in various subgroups of schizophrenic patients in studies of **Nishi et. al., 2014**[13] and **Muntjewerrif et. al., 2006**[14]. The later also estimated that the risk of schizophrenia may increase by 70% if Hcy level will be increased by 5 µmol. Contradictory results have however been reported by **Virgos et. al**., 1999[15] who found plasma Hcy levels no different in schizophrenic inpatients and comparison subjects.

Previous research by **Neeman G et. al., 2005**[16], has suggested that amino acid disturbances may contribute significantly to the pathophysiology of schizophrenia. Similar findings have been demonstrated by **Sumiyoshi T et. al.**, 2004[17]. Further, study by **Levine J et. al., 2002**[18] indicates that low glycine and high Hcy levels may coexist in patients with schizophrenia. In another study by **Levine J et. al., 2006**[19], have reported significant negative correlations between blood folic acid and Hcy. Significant negative correlations between vitamin B12 levels and Hcy have also been reported by **Stahl et. al., 2005**[20]. Moreover, **Haidemenos et. al., 2007**[21], reported that increased Hcy demonstrated a strong negative association with the reduced vitamin B12.

The above findings can possibly be due to a genetic polymorphism related to Hcy metabolism which might be manifested in schizophrenic patients & might be responsible for interaction with other factors for elevated Hcy22. According to few studies done by **Buckley et. al., 2007**[23]; **Shovel & Weizman, 2005**[24]; altered functions of neurotrophic factors and antioxidant genes play a vital role in brain development and function of schizophrenia. Furthermore, according to **Picker and Coyle, 2005**[25] low internal folate and high Hcy levels are suggested to increase the risk for developing schizophrenia. A study by **Kroll et. al., 2007**[26] suggested liver dysfunction to be largely contributing to a number of metabolic abnormalities in patients of schizophrenia. This observation is important since liver plays a vital role in storage & metabolism of micronutrients, particularly vitamin B12 & perhaps also folate.

In a large cohort study, **Dey AB & Soneja S, 2001**[27] also reported depression to be the most common psychiatric diagnosis among the elderly subjects. Depressed mood can be a common secondary observation in patients suffering from other pathological conditions. In a review, data pooled from several studies conducted across the world have reported prevalence rates of depression as high as 19.3% to 23.3% among stroke patients. Improved mood has been observed in patients following administration of antidepressants in such patients[28].

According to previous researches depression is a symptom and risk factor for heart disease[29]. Although, the pathogenesis of depression in heart disease is not clearly understood, possible mechanisms may include cerebral infarcts or drugs used to treat depression and heart disease, including diuretics and anticonvulsants[30].

Homocysteine has been reported to cause alteration of neurotransmitter which might also cause depression. Studies that directly measure neurotransmitters have demonstrated association between homocysteine and psychiatric disorders[31].

CONCLUSION

The present study has demonstrated that the plasma Hcy levels are significantly higher in patients of depression and schizophrenia. Therefore, the study recommends evaluation of S Hcy levels in patients with psychiatric manifestations. Radiological screening of depressed and schizophrenic patients for vascular disease is also suggested.

The study recommends further research on the association of plasma Hcy levels with concentration of vitamin B12 and folic acid in patients of depression and schizophrenia. Thorough researches should be conducted to evaluate the role of metabolic derangements on psychiatric manifestations and vice versa which can be helpful in planning better treatment protocols.

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