ejpmr, 2017,4(06), 305-309

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

COGNITIVE DEFICITS ASSOCIATED WITH HYPERHOMOCYSTEINEMIA IN SC AND ST CHILDREN OF SONBHADRA DISTRICT OF EASTERN UTTAR PRADESH

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Article Received on 30/03/2017 **Article Revised on 20/04/2017** **Article Accepted on 10/05/2017**

ABSTRACT

Introduction: Cognitive is concerned with different domain of brain function like learning, memory, perception, concept, language, attention, metacognition, thinking, judgement etc. Over the decades a wide range of cognitive deficits has been observed in Indian children. There are multifaceted factors responsible for cognitive impairment in children includes nutritional deficiencies, genetic expression, prenatal and post-natal influences, behavioural influences as well as environmental influences. ‘‘Hyperhomocysteinemia’’ terms indicates increase in the elevated levels of homocysteine (Hcy) than the normal levels (5-15 µmol/l). Numerous longitudinal and cross sectional studies revealed elevated levels of total plasma homocysteine is associated with cognitive impairment. **Objective:** Therefore, the present study was designed to investigate the relationship between blood plasma homocysteine levels and cognitive functions across different age groups of general, schedule caste and schedule tribe children’s of Sonbhadra district. **Materials & Methods:** Recruitment of subjects between the ages of 4-11 years was selected as part of comprehensive field study in different areas of Eastern Uttar-Pradesh purposively Sonbhadra. The district is divided into three groups and quota sample method was used to decide the number of study subjects to each groups and the selection of these subjects were carried out by convenience sampling. Biochemical examinations including vitamin $B_{12,}$ folate and vitamin B_6 levels were done by using enzyme immunoassay kit. The obtained results were then statistically analysed. **Results:** Our observation of the present data implies that SC and ST children show reduced levels of vitamin $B_{12,}$ vitamin B_6 and folate thereby results in elevated concentration of total homocysteine in blood plasma (tHcy). **Conclusion:** Therefore based on the result it has been concluded that by increasing dietary supplementation of folic acid, vitamin B_{12} and vitamin B_6 explore as a method for reducing the concentration of homocysteine.

KEYWORDS: homocysteine, folate, vitamin B_{12} and vitamin $B_{6.}$

INTRODUCTION

Cognitive is concerned with different domain of brain function like learning, memory, perception, concept, language, attention, metacognition, thinking, judgement etc. Over the decades a wide range of cognitive deficits has been observed in Indian children. There are multifaceted factors responsible for cognitive impairment in children includes nutritional deficiencies, genetic expression, prenatal and post-natal influences, behavioural influences as well as environmental influences.

‘‘Hyperhomocysteinemia’’ terms indicates increase in the elevated levels of homocysteine (Hcy) than the normal level (5-15 µmol/l).[1] Numerous longitudinal and cross sectional studies revealed that elevated levels of total plasma homocysteine levels in peripheral blood is associated with a wide array of illness, includes stroke[2-5], coronary heart disease[2,6,7], artery atherosclerosis[8,9], cognitive impairment and dementia.[10-12] Additionally, researchers also elucidated the relationship between homocysteine and cognitive impairment. In the early 1962, Gerritsen J. et al. reported the first confirmation of elevated total plasma homocysteine concentrations in a group of mentally disturbed children.[13] Regland et al. also emphasized that high plasma homocysteine concentrations is responsible for adapting cognitive impairment.[14] Thus to maintain the normal levels of homocysteine in blood plasma nutritional status i.e vitamin B_{12} (cobalamin), vitamin B_6 (pyridoxine) and

vitamin B_9 (folate) plays a significant role whereas scarcity of these vitamins results in elevated homocysteine. Numerous studies have reported vitamin-B therapy helps in lowering homocysteine levels thereby also improve cognitive performance.

Homocysteine as a risk factor for cognitive impairment-

There are numerous factors that may account for cognitive impairment, researchers revealing the magnitude of the effect of homocysteine in impaired cognitive function.

Homocysteine and glutamate receptors

It is well known fact that glutamate is an excitatory neuro-transmitter in brain associated with learning and memory. An elevated level of total plasma homocysteine concentrations is highly neurotoxic. Hyperhomocysteinemia is glutamate receptor agonist N-Methyl-D-aspartate **(**NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). NMDA and AMPA are two essential glutamate receptors, hyperhomocysteinemia overstimulate the NMDA receptors and thus disrupt the normal chemical equilibrium of glutamate neurotransmitter.[15]

Homocysteine and oxidative stress

Vitamin B_{12} deficiency is responsible to cause pernicious anemia, peripheral neuropathy, lack of energy and poor memory. Hence, if the vitamin-B levels is suboptimal, homocysteine levels rise which increases oxidative stress and as a result accountable to cause brain lipid peroxidation.[16][17]

Homocysteine and hypomethylation

Methylation is one of the obligatory process for the assembly and catabolism of several neurotransmitters and also indispensable for DNA-methylation. In the remethylation pathway of homocysteine vitamin-B_{12} and folate is essentially required.[18,19] Decrease in concentration of vitamin-B_{12} and folate in blood plasma disturb the homocysteine remethylation process thereby results in decreased SAM and increased SAH thus causing to neuronal damage which affects brain.[18,19]

Therefore, the present study was designed to investigate the relationship between blood plasma homocysteine levels and cognitive functions across different age groups of general, scheduled caste and schedule tribe children's of Sonbhadra district of Eastern Uttar Pradesh.

MATERIALS AND METHODS

Recruitment of subjects between the ages of 4-11 years was selected as part of comprehensive field study in different areas of Eastern Uttar-Pradesh purposively Sonbhadra. The district is divided into three groups and quota sample method was used to decide the number of study subjects to each groups and the selection of these subjects were carried out by convenience sampling. The study included 210 subjects, 70 were general, 70 were schedule caste and 70 were schedule tribe children. All the subjects fall as per the mentioned exclusion and inclusion criteria's of the study protocol. Participants gave informed consent to participate in the study in accordance of ethical standards. The study was approved by ethical committee of Banaras Hindu University, Varanasi.

Biochemical Tests

Biochemical examinations of the participants were done by using commercially available enzyme linked immune sorbent assay (ELISA). Blood samples were collected and immediately kept in ice bag after then homocysteine (Hcy) levels were assessed. Plasma homocysteine levels were determined using Human-Hcy Cat. No. QY-E01223 ELISA double sandwich method. Levels of vitamin B_{12}, vitamin B_9 and vitamin B_6 were also assessed by ELISA method.

Cognitive assessment

All the three groups of children were assessed for cognitive function using attention span apparatus and audio-visual reaction time (Medicaid system, Chandigarh, India).

Statistical analysis

All results were statistically analysed and were expressed in mean ± SD. Difference between samples were analysed by using ANOVA.

RESULT

In the present study a total of 210 subjects, 70 general class, 70 scheduled caste and 70 schedule tribe children were enrolled. Table 1 represent the values expressed as mean ± standard deviation of plasma homocysteine, serum folate, vitamin B_{12} and vitamin B_6 in general, scheduled caste and schedule tribe children respectively.

Table 1 demonstrates the circulating concentration of serum homocysteine, folate, vitamin B_{12} and vitamin B_6 in blood plasma. We observed a significant fall in serum folate, vitamin B_{12} and vitamin B_6 levels in scheduled caste and scheduled tribe children when compared with the mean of general class children. Folate, vitamin B_{12} and vitamin B_6 act as substrate and enzyme respectively which influences the homocysteine metabolism. As a result we can assume that reduced in the levels of folate, vitamins B_{12} and B_6 will elevate the levels of homocysteine in both the SC and ST groups.

Table: 1. Mean and standard deviation of homocysteine, folate, vitamin B_{12} and vitamin B_6 levels in normal, SC and ST children.

Parameters	General (N=70)	Schedule caste (N=70)	Schedule tribe (N=70)	F-value	p-value
Homocysteine (µmol/L)	8.12±3.2	25.76±5.07	32.15±3.7	655.39	0.000
Serum folate (nmol/L)	34.29±2.04	10.22±3.01	6.38±3.75	1785.75	0.000
Vitamin B_{12} (pg/mL)	546.98±5.3	173.86±8.9	112.73±4.6	90,327.7	0.000
Vitamin B_6 (µg/L)	47.1±5.6	4.2±1.4	3.8±2.0	3984.48	0.000

Table: 2. Post-hoc method is applied between the groups for every single parameters to see the level of significance.

Parameters	Groups	q(calculated)	p-value
Homocysteine ((µmol/L)	Normal Vs SC	50.63	<0.001
	Normal Vs ST	68.97	<0.001
	SC Vs ST	18.34	<0.001
Serum folate (nmol/L)	Normal Vs SC	50.78	<0.001
	Normal Vs ST	58.89	<0.001
	SC Vs ST	8.10	<0.001
Vitamin B_{12} (pg/mL)	Normal Vs SC	1723.81	<0.001
	Normal Vs ST	2006.23	<0.001
	SC Vs ST	282.42	<0.001
Vitamin B6 (µg/L)	Normal Vs SC	106.82	<0.001
	Normal Vs ST	107.81	<0.001
	SC Vs ST	0.99	>0.05

Table 3 represents the attention span of general, scheduled caste and schedule tribe children. From the given table we can see that tribal children performance was poorer than the both scheduled caste and general class children. General class children gave the responses more quickly than the SC and ST children. Children gave responses more quickly in decreasing order as in this they easily catch the point when light started vibrating.

Table: 3 Mean and standard deviation of attention span in both increasing and decreasing order of general, SC & ST children.

	Normal	Schedule caste	Schedule tribe	F-value	p-value
Increasing order	45.12±3.2	58.56±10.2	62.67±7.23	106.23	0.000
Decreasing order	41.03±2.2	28.83±8.89	28.72±5.98	87.88	0.000

Table: 4. Post hoc method is applied between the groups for both increasing and decreasing parameters to see the level of significance.

Parameters	Groups	q(calculated)	p-value
Increasing order	Normal Vs SC	70.69	<0.001
	Normal Vs ST	92.31	<0.001
	SC Vs ST	21.61	<0.001
Decreasing order	Normal Vs SC	54.41	<0.001
	Normal Vs ST	54.90	<0.001
	SC Vs ST	.49	>0.001

DISCUSSION

Several reports documented that elevated concentration of total homocysteine in blood plasma is associated as a risk factor for cardiovascular disease (CVD)[20, 21], cerebrovascular disease[22-25], obesity[26, 27] dementia[28-30], brain atrophy[31,32], oxidative stress[33, 34] hyperhomocystenemia.[35] Many findings have supported that increased in the concentration of homocysteine is considered risk factor for cognitive impairment. In the year 1983 Godwin et al. reported nutritional status play vital role in cognitive impairment.[35] Hence homocysteine is regarded as a marker for cognitive impairment. In the year 2007, Clarke et al. conducted study on 1648 subject's age of 75 years (MMSE 26.2). Ten years of Clarke et al. findings supported there is a direct correlation between homocysteine and cognitive development, between holoTC and cognitive development and also between methylmalonic acid

(MMA) and cognitive development. Increased levels of methylmalonic acid (MMA) and holoTC consider as a biomarker which results in reducing vitamin-B_{12} level. Doubling-up of holoTC levels results in 30% fall in cognitive function, while elevation of total plasma homocysteine twice than the normal levels results in more than 50% fall of cognitive function.[36] Later on in the same year 2007, Haan et al. also revealed the association between homocysteine, folate and cobalamine and their role in cognitive impairment in 1405 participants.[37] The present study was therefore designed to determine the levels of circulating total plasma homocysteine concentration, serum folate, vitamin B_{12} and vitamin B_6 in order to explore relationship among them. Above results clearly indicate that there is a strong interrelationship between cognitive impairment homocysteine concentration, folate, vitamin B_{12} and vitamin B_6.

Blood plasma homocysteine levels is significantly increased (p-value 0.000) in case of SC and ST children when compared to general class. Our findings also interprets that levels of homocysteine is higher in ST children than SC and general class children, the data of our study are compatible with previous studies. Thereby reduce in the levels of folate, vitamin B_{12} and B_9 is extensively considered as a marker of elevated total homocysteine concentration.

CONCLUSION

The results collectively indicated that blood plasma homocysteine levels were found to be negatively associated with vitamin $B_{12,}$ vitamin B_6 and serum folate levels. Our observation of the present data implies that reduction in the levels of vitamin $B_{12,}$ vitamin B_6 and folate in SC and ST children play a pivotal role in the elevation of total homocysteine in blood plasma (tHcy) because relative deficiencies disrupt the remethylation process of homocysteine and thus results in homocysteine accumulation. Therefore based on the result it has been concluded that by increasing dietary supplementation of folic acid, vitamin B_{12} and vitamin B_6 explore as a method for reducing the concentration of homocysteine.

ACKNOWLEDGEMENT

The authors extend their sincere thanks to the Department of Science and Technology (DST), Government of India, for supporting this study. The authors are also thankful to the study subjects for participating in the study.

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