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Original Research Article

A correlative study of homocysteine levels and dementia: an Indian perspective

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ABSTRACT

Background: The prevalence of dementia is increasing worldwide and with India experiencing an epidemiological transition with increasing ageing population, the prevalence in India is expected to double by 2030 adding to the already high burden of significant health care costs and caregiver fatigue. Indian population has a higher burden of elevated homocysteine levels due to multiple factors. However, studies correlating the homocysteine levels and severity of dementia in the Indian subcontinent is lacking. This study is aimed to analyse the diagnostic utility of serum total homocysteine in dementia and to examine the association between serum total homocysteine levels and severity of dementia.
Methods: This was a cross-sectional hospital-based study on patients attending neurology out-patient department who satisfied the DSM-V criteria. Each participant underwent an interview of general health and function followed by a standard assessment including medical history, physical and neurological examination as well as a neuropsychological battery.
Results: A total of 30 patients fulfilling the DSM-Vcriteria for Dementia were included in the study. Increasing S. Homocysteine levels were associated with lower neuropsychological compound scores with MMSE score of 20.78±2.98 and ACE-3 score of 77.40±5.60 in patients with Serum Homocysteine less than 22 Umoles/L and 18.85±2.50 and 75.55±5.06 respectively in patients with serum homocysteine levels above 22 Umoles/L. However, there was no statistically significant correlation between neurocognitive scores and serum homocysteine levels (p value 0.06 for MMSE and 0.19 for ACE-3). Also, no correlation was found between severity of dementia and serum homocysteine levels with $p \geq 0.05$ and Pearson's correlation coefficient $r=0.06$.
Conclusions: This study shows no significant association between serum total homocysteine levels and severity of dementia. Thus, the association of homocysteine as an independent risk factor with the diagnosis and severity of dementia needs to be re-evaluated as it might undermine the multiple mechanisms underlying the pathogenesis of dementia.

Keywords: Homocysteine, Dementia, Small vessel disease, Vascular risk factors

INTRODUCTION

Dementia is a disease of the elderly, which exhibits progressive loss of memory and other cognitive faculties leading to impairment of daily activities. It has become a public health priority by imparting remarkable health care costs along with significant caregiver burden. The diagnosis of Major Neurocognitive Disorder or Dementia according to Diagnostic and Statistical Manual of Mental Disorders-Vth edition (DSM-V) requires substantial impairment to be present in one or more cognitive domains, sufficient to interfere with independence in day to day activities.[1] The prevalence of dementia is increasing worldwide, rising exponentially with age and

doubling every five years after the age of 65. India is witnessing an epidemiological transition with an increase in the aging population. It is estimated that out of the 70 million senior citizens in our country, around four million are affected by dementia and these numbers are expected to double by 2030.[2]

Many hypotheses have been put forward regarding the etiopathogenic mechanisms in Alzheimer's disease. In addition to the amyloid hypothesis, the vascular hypothesis has emerged as an alternative in the pathophysiology of Alzheimer's disease. Vascular pathology plays a significant role in the development and progression of Alzheimer's disease and the risk of developing the disease is enhanced by the vascular risk factors. Cardiovascular risk factors may accelerate the risk of cognitive decline by diminishing cerebral blood flow resulting in capillary hypoperfusion and accelerated production of β-amyloid. These factors eventually culminate in neuronal dysfunction.[3,4]

One of the important risk factors for cerebrovascular and cardiovascular diseases is hyperhomocysteinemia.[5,6] Elevated serum homocysteine levels have been attributed for neurotoxicity along with vascular lesions in Alzheimer's disease.[7] Various cross-sectional studies have reported that hyperhomocysteinemia was associated with a greater prevalence of cognitive deficits and dementia.[7,8] Homocysteine has been suggested as a diagnostic marker for Alzheimer's disease lately.

When compared to the western population, our population has a higher burden of elevated homocysteine levels due to multiple factors. This may be one of the elements responsible for an increased incidence of cerebrovascular disease.[9]

Several studies have been conducted in other countries to study the correlation between dementia and homocysteine levels. Such a study among Indians is lacking. The objective of the present study was to examine the association between serum total homocysteine levels and severity of dementia in a sub set of Indian population

METHODS

This was a cross-sectional hospital-based study. Patients attending neurology out-patient department who satisfied the DSM-V criteria of Dementia were included. Each participant underwent an interview of general health and function followed by a standard assessment. This included medical history, physical and neurological examination as well as a neuropsychological battery. Baseline data was collected from 2019 through 2021.

Diagnosis of dementia

Dementia was diagnosed by a consensus of neurologists, neuropsychologists and psychiatrist based on the criteria of Diagnostic and Statistical Manual of Mental Disorders, fifth edition. Consistent with the standard criteria, patients diagnosed with dementia were required to have: memory complaint; objective impairment in at least one cognitive domain based on the average of the scores on the neuropsychological measures within that domain and a 1.5-SD cut off using normative corrections for age, years of education, ethnicity, sex and impaired activities of daily living.

Cognitive measures

The battery of cognitive tests administered to the subjects included Mini Mental State Examination (MMSE), Addenbrooke's cognitive examination III and Clinical Dementia Rating Scale.

Laboratory tests

Baseline investigations included complete blood counts, erythrocyte sedimentation rate (ESR), renal parameters, fasting glucose and glycosylated haemoglobin (HbA1C). In addition, C- reactive protein (CRP), Triglycerides (TGL), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Thyroid stimulating hormone (TSH), Folic acid, and Vitamin B12 levels were obtained.

For Total serum homocysteine levels,10 mL fasting blood sample was collected in EDTA- coated vial between 8 and 9 am after 12 h fasting. Blood sample was centrifuged at 10,000 rpm for 10 min and plasma was separated. The sample was preserved at -40□C till analysed. Total plasma homocysteine was estimated by enzymatic assay using Roche/Hitachi cobas c311 analyser.

MRI brain

Cranial MRI scanning was performed in all participants with 3-Tesla scanner. Four high- resolution axial sequences were obtained: T1-weighted sequence, proton density–weighted sequence, fluid-attenuated inversion recovery sequence, and T2-weighted gradient echo sequence. No contrast material was administered.

Neuroimaging features of cerebral small vessel disease were analysed and the cSVD sum score was arrived according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE).[10] The presence of four MRI markers (white matter hyperintensities, lacunes, cerebral microbleeds, and perivascular spaces; range, 0–4) were used in deriving this score individually.

Duplex ultrasonography

Using a 7.5 MHz linear array transducer and a duplex scanner, carotid arterial systems on both sides were examined for the presence of plaques. The presence of plaque was defined as localized echo structure(s) encroaching into the arterial lumen of at least 50% of the surrounding Intima-media thickness value.[11] Plaque score

(PS) was rated as grade 0 for normal or without plaque, 1 point for one small plaque with diameter stenosis <30%, 2 points for one medium plaque with 30–49% diameter stenosis or multiple small plaques, 3 points for one large plaque with 50–99% diameter stenosis or multiple plaques with ≥1 medium plaques, and 4 points for 100% occlusion.[12]

Statistical package for social sciences (SPSS0 version 15.0 for windows was used for the testing of data. The confidence interval and significance level for this study was considered 95% and p<0.05 respectively. Two-talled t-test was performed for comparing samples and arriving at p-values (95% confidence level). Two factor ANOVA was used to compare multiple samples. All correlation between variables are based on Pearson's correlation coefficients.

Ethical consideration

The research has been authorized by the Institutional Ethical Committee of JSS Medical College.

RESULTS

Demographic and clinical data

A total of 30 patients diagnosed with dementia, satisfying the inclusion criteria were included in this study. Among these 30 patients, 21 (70%) were males and 9 (30%) were females. Mean age of the patients was 70.67±4.4 years, with the youngest patient being 62 years and the oldest being 78 years of age. The average duration of illness among patients was 22.4±6.41 months. 16(53.33%) patients were found to be hypertensives and 15(50%) patients were diabetics on treatment. Eight subjects (26.67%) were found to have both diabetes and hypertension.

The mean MMSE score was 19.47±2.71 in our study population. Mean ACE-3 score was 76.17±5.13. The mean CDRS-SOB score was 6.78±2.66. The mean cVSD score across our study population was 2.33±0.94. Carotid intimal medial thickness was 0.47±0.23mm. Plaque score was 2.03±0.835.

Correlation of homocysteine levels with cognitive and neuroimaging scores

Mean serum homocysteine level was 27.36±9.53 Umoles/L which is slightly above the normal range (6-22 Umoles/L). Patients with a higher serum homocysteine level were more likely to be men, older and active smokers as compared to those with a lower serum homocysteine level. The mean values of systolic and diastolic blood pressure were 140.80±17.69 mmHg and 90.80±8.34 mmHg respectively in subjects whose homocysteine levels were below 22 Umoles/L. Mean systolic and diastolic blood pressure were 132.30±20.88 mmHg and 86.90±10.69 mmHg in second group whose homocysteine was above 22 Umoles/L.

Table 1: Baseline characteristics of the study population.

Characteristics	Mean (SD)	Range
Socio demographic factors		
Age, years	70.67±4.4	62-78
Male (n)	21	
Female (n)	9	
Education (n)	<10 years:22; >10 years:8	
Hypertension (n)	16, (M:11, F:5)	
Diabetes Mellitus (n)	15, (M:7 F:8)	
HTN and DM (n)	8 (M:3 F:5)	
Active smokers (n)	14 (M:14, F:0)	
SBP (mmHg)	135.13±19.64	
DBP (mmHg)	88.2±9.83	
Cognitive functions		
MMSE	19.47±2.71	15-24
ACE -3	76.17±5.13	65-84
CDRS-SOB	6.78±2.66	3-12
Neuroimaging and doppler		
CSVD Score	2.33±0.942	1-4
CIMT (mm)	0.47±0.23	0.12-0.9
Plaque Score	2.03±0.835	1-4
Biochemical test		
Haemoglobin (mg/dl)	10.51±1.228	7-12.5
S. Urea (mg/dl)	36.06±12.46	22-64
S. Creatinine (mg/dl)	0.95±0.24	0.6-1.4
T. Cholesterol (mg/dl)	170.2±34.32	123-263
HDL (mg/dl)	59.9±17.35	27-94
LDL (mg/dl)	94.06±31.14	44-165
TGL (mg/dl)	117.83±28.69	80-188
S. Homocysteine (Umoles/L)	27.36±9.53	12-46
S. Vitamin B12 (pg/ml)	267.9±162.297	112-812
S. Folic acid(ng/ml)	15.56±5.9	3.5-30.1
HbA1c	7.11±1.16	5.7-10.3

This was not statistically significant. The mean values of serum vitamin B12 and folic acid was lower in the group B but were not statistically significant with a p value of 0.08 and 0.06 as shown in Table 2.

Increasing S. Homocysteine levels were associated with lower neuropsychological compound scores. We found that MMSE was 20.78±2.98 in group A and 18.85±2.50 in group B with a p value of 0.06. ACE-3 scores across the group were higher in the second group with a p value of 0.19.

We found no significant differences in cSVD (cerebral Small Vessel Disease) score, plaque score and CIMT (Carotid Intima-Media Thickness) between the groups.

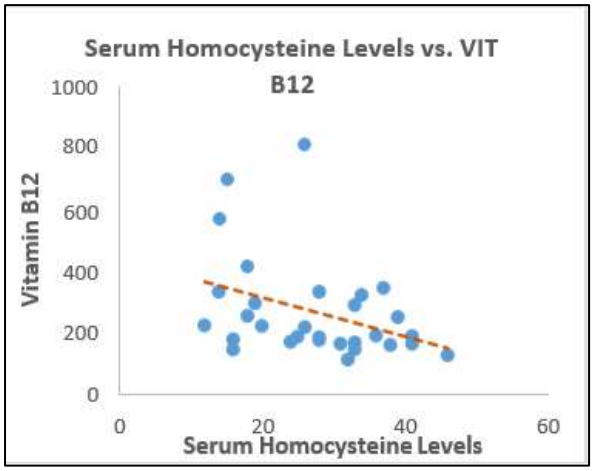

Figure 1: Correlation of Vitamin B12 levels and Serum Homocysteine levels. The correlation coefficient is -0.37 and p<0.05.

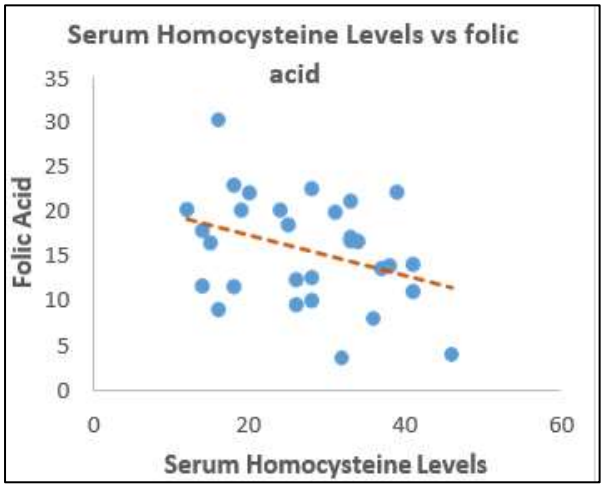

Figure 2: Correlation of Folic acid levels and Serum Homocysteine levels. The correlation coefficient is -0.35 and p<0.05.

We observed that there was small inverse correlation of systolic blood pressure and diastolic blood pressure with serum homocysteine levels exhibiting r value of -0.27 and -0.31 respectively. There was medium correlation between vitamin B12 levels, serum folic acid and serum homocysteine levels with r value of -0.37 and -0.35 respectively. There was no correlation between neurocognitive scores and serum homocysteine levels. cSVD score, plaque score and CIMT score also had weak correlation with serum homocysteine levels.

Correlation of severity of dementia with cognitive scores, neuroimaging scores, homocysteine levels, folic acid levels and serum vitamin B12 levels

We observed that with increasing severity of dementia as reflected with the CDRS-SOB score, there was significant decline in neurocognitive scores like MMSE and ACE-3 scores with a p<0.001. We also found that low scores in cognitive domains like visuospatial, memory and language correlated well with the severity of dementia with p<0.001. However, in our study no significant difference of serum homocysteine, serum vitamin B12 levels, folic acid levels were observed between the groups as shown in Table 3.

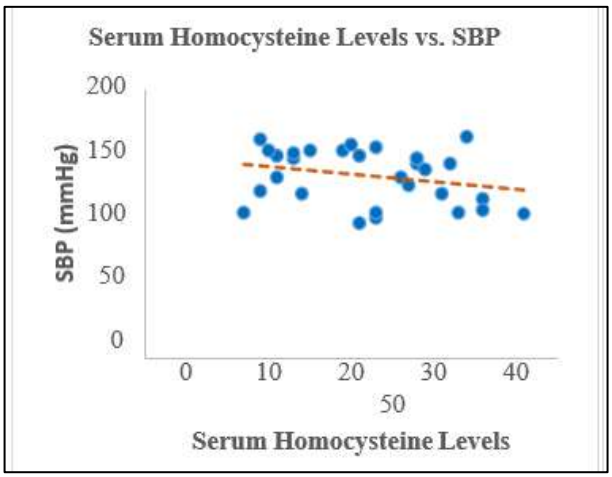

Figure 3: Correlation of Systolic Blood Pressure and Serum Homocysteine levels. The correlation coefficient is -0.27 and p<0.05.

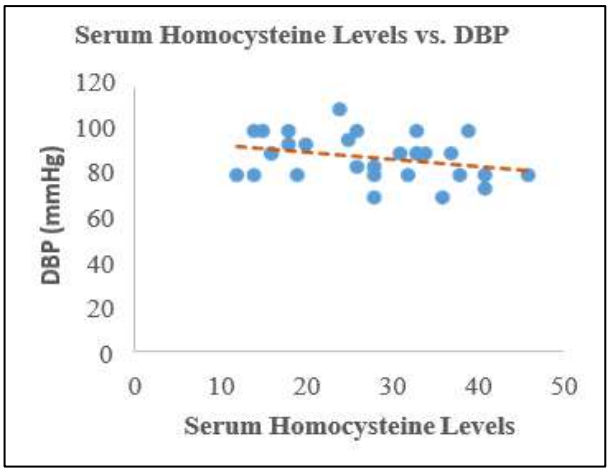

Figure 4: Correlation of Diastolic Blood Pressure and Serum Homocysteine levels. The correlation coefficient is -0.31 and p<0.05.

Neuroimaging scores revealed that plaque score was significantly higher in patients with severe dementia with a p value of <0.05. However, cVSD score and CIMT were not statistically significant.

There was strong negative correlation of MMSE and ACE-3 scores with CDRS-SOB scores with r value of -0.69 and -0.71 respectively. Memory, fluency and

visuospatial components of ACE-3 had a strong correlation with CDRS-SOB scores with r value of -0.7, -0.62 and -0.48 respectively. No correlation was found between serum homocysteine levels and severity of dementia. Plaque score demonstrated a weak negative correlation with CDRS-SOB score with r value of -0.25. There was no correlation between cVSD and CIMT with CDRS-SOB score.

Table 2: Comparison between normal and elevated serum homocysteine levels.

Characteristics	Serum homocysteinelevels		P value	r (Pearson's Correlation Coefficient)
	Group A (<22)	Group B (>22)		
N	10	20		
Hypertension	6 (60%)	10 (50%)		
Diabetes mellitus	3 (30%)	12 (60%)		
Active smoking	5 (50%)	9 (45%)		
Age, years	68.70±3.86	71.65±4.53	0.04	0.20
SBP, mmHg	140.80±17.69	132.30±20.88	0.13	-0.27
DBP, mmHg	90.80±8.34	86.90±10.69	0.14	-0.31
MMSE	20.70±2.98	18.85±2.50	0.06	-0.21
ACE-3	77.40±5.60	75.55±5.06	0.19	-0.15
CDRS-SOB	6.65±3.38	6.85±2.40	0.43	0.06
CVSD score	2.60±0.84	2.20±1.01	0.13	-0.27
Plaque score	2.20±1.03	1.95±0.76	0.25	-0.23
CIMT	0.484±0.284	0.456±0.212	0.66	-0.03
S. Homocysteine (Umoles/L)	16.20±2.53	32.95±6.10	<0.001	X
T. Cholesterol (mg/dl)	170.90±38.24	169.85±33.25	0.47	0.01
HbA1c	6.84±1.13	7.24±1.19	0.19	-0.03
S. VitaminB12 (pg/dl)	333.50±178.61	235.10±151.92	0.08	-0.37
S. Folic acid (ng/dl)	18.12±6.32	14.29±5.57	0.06	-0.35

Table 3: Comparison between groups with increasing severity of dementia.

Characteristics	CDRS score			F value	P value	r (Pearson's Correlation Coefficient)
	<4.5	4.6-9	9.1-15			
N	10	15	5			
Age	69.6	72.57	66.8			-0.09
Males/females	8/2	9/6	4/1			
Hypertension	5	8	3			
Diabetes mellitus	4	9	2			
Active smoking	6	6	2			
SBP	136.4±21	134.4±21.1	134.8±18.4	0.03	0.97	0.01
DBP	88±8.9	88.4±11	88±11	0.005	0.99	0.07
MMSE	22.6±1.07	17.73±1.87	18.4±1.82	27.71	<0.001	-0.69
ACE-3	80.3±2.98	75.93±3.86	68.6±3.36	18.49	<0.001	-0.71
Attention	14.5±1.08	13.33±1.11	13.8±1.48	3.00	0.07	-0.20
Memory	18.9±0.99	16.53±1.41	15±1.73	16.44	<0.001	-0.71
Fluency	11±0.67	9.87±0.83	9±1.22	10.23	<0.001	-0.62
Language	21.9±1.45	22.47±0.83	20.6±1.52	4.68	0.02	-0.23
Visuospatial	13.6±1.35	13.6±2.06	9.8±0.84	10.30	<0.001	-0.48
CVSD score	2.5±0.97	2.2±1.01	2.4±0.89	0.29	0.75	-0.10
CIMT	0.42±0.19	0.48±0.26	0.52±0.26	0.30	0.74	0.16
Plaque score	2.5±0.85	1.67±0.72	2.2±0.84	3.51	0.04	-0.25
S. Homocysteine (Umoles/l)	25.5±8.03	28.87±10.80	26.6±9.37	0.37	0.69	0.06
S.Vitamin B12 (pg/dl)	275.9±199.54	247.73±163.75	312.4±99.77	0.29	0.75	0.05
S. Folic acid (ng/dl)	13.66±5.56	15.01±5.43	21.06±6.41	3.02	0.06	0.39

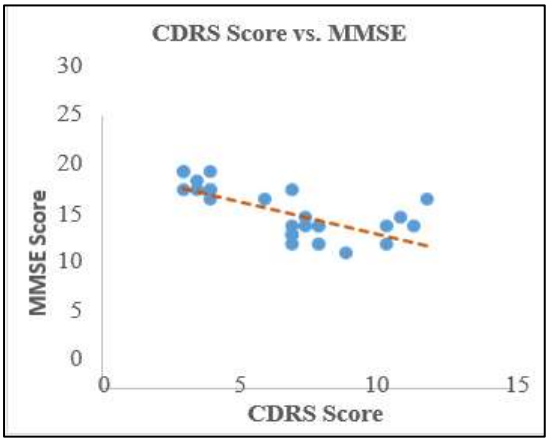

Figure 5: Correlation of MMSE and CDRS score. The correlation coefficient is -0.69 and p<0.001.

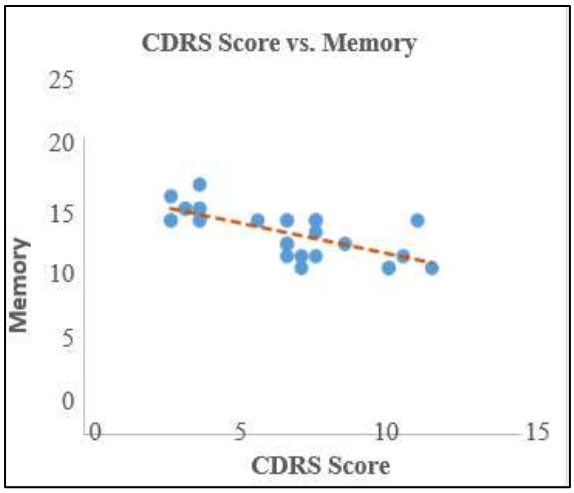

Figure 6: Correlation of Memory score on ACE-3 and CDRS score. The correlation coefficient is -0.71 and p<0.001.

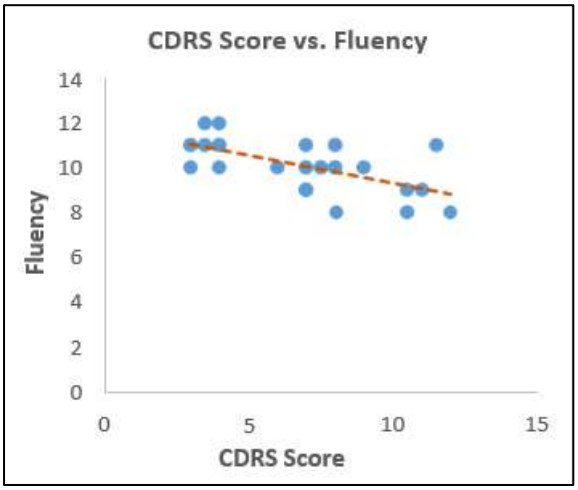

Figure 7: Correlation of Fluency score on ACE-3 and CDRS score. The correlation coefficient is -0.62 and p<0.001.

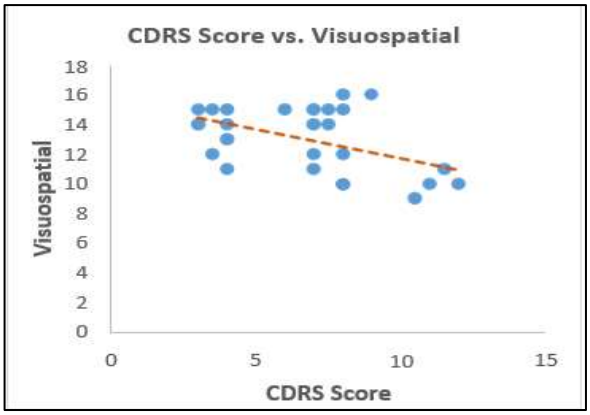

Figure 8: Correlation of Visuospatial score on ACE-3 and CDRS score. The correlation coefficient is -0.48 and p<0.001.

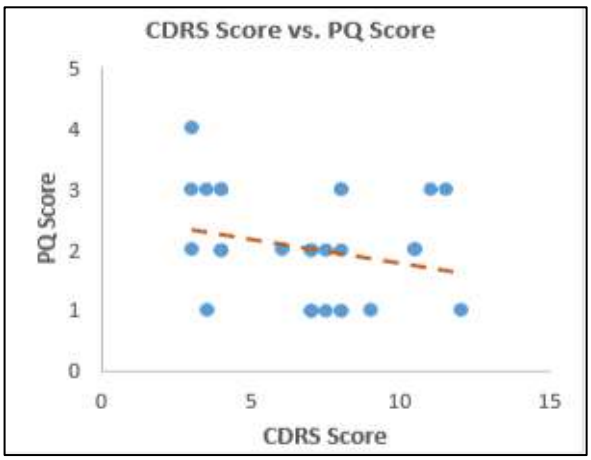

Figure 9: Correlation of Plaque score and CDRS score. The correlation coefficient is -0.25 and p<0.05.

DISCUSSION

Correlation of homocysteine levels with cognitive and neuroimaging scores

This study was conducted to investigate the correlation of homocysteine levels with severity of dementia. Although the correlations of homocysteine with cognitive functions have been previously investigated, there have been very few studies in the Indian subcontinent. The results of previous studies are discordant, but most of the studies demonstrated that high homocysteine levels correlated with decreased cognitive functions.[13,14] Several plausible biological mechanisms may explain the relationship between total homocysteine levels and cognitive function. Brain damage by homocysteine can be attributed to multiple mechanisms such as disturbed protein methylation, promotion of calcium influx, and tau protein accumulation, all contributing to apoptosis and neuronal death.[15]

Contrarily, several studies have shown weak or no correlation between homocysteine levels and cognitive

decline. In the prospective community based study of elderly subjects by Kalmijn et al, there was no significant association of elevated homocysteine levels with cognitive impairment which is similar to our study.[16] Arioğul et al also found no significant relation between the cognitive functions and serum homocysteine levels.[17] In a study by Chen et al, the exposure response relationship between serum homocysteine levels and dementia was not found at the low end of serum homocysteine levels but only within range of relatively high concentration showing a non-linear association.[18] This could be another plausible explanation for the lack of statistically significant correlation between serum homocysteine levels and dementia in our study.

Cerebral small vessel disease (cSVD) primarily affects the small perforating arteries, which perfuse the deep brain structures, the meningeal space, and the white matter.[19] cSVD progression leads to subcortical vascular dementia, one of the most frequent forms of degenerative disorders. Its role in Alzheimer's Disease pathology is under intense research.[20,21] In our study we found that elevated homocysteine levels did not show a correlation with cVSD and major atherosclerotic disease. Gunstad et al also found no significant association between homocysteine levels and cSVD.[22] Our study being cross sectional with a single homocysteine level of dementia patients collected at baseline, could be a possible limitation to evaluate a relationship between homocysteine levels and cSVD.

In our study there was weak correlation of homocysteine levels with plaque score and CIMT. Li et al also concluded in their study among rural population in China that there was no significant correlation between elevated homocysteine level and carotid atherosclerosis.[23] In a sub study of VITAmins TO Prevent Stroke (VITATOPS) trial and Atherosclerosis and Folic Acid Supplementation Trial (ASFAST), there was no significant difference in CIMT by Vitamin B complex and Folic acid supplementation respectively.[24,25] These findings show that the role of homocysteine in cardiovascular events and atherosclerosis may be overvalued. These results coupled with our data suggest that homocysteine may not have significant effect on carotid atherosclerosis.

We found an inverse correlation between blood pressure and serum homocysteine levels which was similar to the study conducted by Sundstorm et al.[26] We also found an inverse correlation of serum vitamin B12 levels and serum folic acid levels with serum homocysteine levels which has been demonstrated in earlier studies by Sadeghian et al and Raina et al.[27,28]

Correlation of severity of dementia with cognitive scores, neuroimaging scores and homocysteine levels

We concluded that higher CDRS-SOB score was associated with lower cognitive scores such as MMSE and ACE-3 similar to study conducted by Takenoshita et al.[9] Quental et al reported lower scores on visuospatial, memory and language functions among patients with higher CDRD-SOB scores which we also observed in our study.[30]

We found that cSVD score did not correlate with the severity of dementia. Although multiple studies have shown significant association between cVSD score and dementia, there is a dearth of study assessing the linear relationship between cVSD and severity of dementia.[31-33] Large sample based, prospective studies are in need for the same.

In our study no significant difference of homocysteine is seen across the various groups with increasing severity of dementia as indicated by increasing CDRS scores. In a longitudinal study by Clarke et al, they noted that serum homocysteine levels did not increase as dementia worsened.[7] Several other studies have also noticed that homocysteine lowering therapies did not show any clinically significant benefit in cognitive impairment.[34-36] Hence, the role of serum homocysteine as an independent risk factor in the progression of dementia is still questionable.

Vascular risk factors and cardiovascular diseases are associated with vascular dementia as well as Alzheimer's disease. Vascular risk factors accelerate atherosclerosis, which in turn is associated with an increased risk for dementia.[37] In our study we found a correlation between severity of dementia and plaque score similar to the study conducted by Oijen et al.[37] Similarly, in the Tromsø study, the average plaque scores were associated with lower scores in all cognitive tests.[38] A study of ultrasound-based strain imaging and cognition assessment conducted on both symptomatic and asymptomatic carotid atherosclerosis patients illustrated that the presence of carotid plaque had a strong relationship with cognitive decline.[39]

The strength of this study is that it is a novel one conducted on the elderly population in South India. Further prospective studies with a large sample size are needed to confirm the association between homocysteine levels and cognitive dysfunction.

CONCLUSION

Dementia is a complex disease which is caused by an interplay of various genetic and environmental risk factors. We conclude that the association of homocysteine as an independent risk factor with the diagnosis and severity of dementia needs to be re-evaluated as this greatly undermines the multiple mechanisms underlying the pathogenesis of dementia.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. American Psychiatric Association: Diagnostic. https://scholar.google.com/scholar_lookup?title=Diagnostic+and+Statistical+Manual+of+Mental+Disorders&publication_year=2013&. Accessed on 25th July, 2020.
2. Alzheimer's & Dementia Help | INDIA. Alzheimer's Association. //www.alz.org/in/dementia-alzheimers-en.asp. Accessed on 25th July, 2020.
3. Rius-Pérez S, Tormos AM, Pérez S, Taléns-Visconti R. Vascular pathology: Cause or effect in Alzheimer disease? Neurol Engl Ed. 2018;33(2):112-20.
4. Rosendorff C, Beeri MS, Silverman JM. Cardiovascular risk factors for Alzheimer's disease. Am J Geriatr Cardiol. 2007;16(3):143-9.
5. Shenoy V, Mehendale V, Prabhu K, Shetty R, Rao P. Correlation of Serum Homocysteine Levels with the Severity of Coronary Artery Disease. Indian J Clin Biochem. 2014;29(3):339-44.
6. The current status of homocysteine as a risk factor for cardiovascular disease: a mini review. https://www.researchgate.net/publication/326241237_The_current_status_of_homocystei ne_as_a_risk_factor_for_cardiovascular_disease_a_mini_review. Accessed on 25th July, 2020.
7. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Arch Neurol. 1998 ;55(11):1449-55.
8. Prins ND, Den Heijer T, Hofman A, Koudstaal PJ, Jolles J, Clarke R, et al. Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study. Neurology. 2002;59(9):1375-80.
9. Hughes K, Ong C. Homocysteine, folate, vitamin B12, and cardiovascular risk in Indians, Malays, and Chinese in Singapore. J Epidemiol Community Health. 2000;54(1):31-4.
10. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12(8):822-38.
11. Touboul P-J, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim Carotid Intima-Media Thickness Consensus (2004–2006). Cerebrovasc Dis. 2007;23(1):75-80.
12. Crouse JR, Harpold GH, Kahl FR, Toole JF, McKinney WM. Evaluation of a scoring system for extracranial carotid atherosclerosis extent with B-mode ultrasound. Stroke [Internet]. 1986;17(2):270-5.
13. Ravaglia G, Forti P, Maioli F, Martelli M, Servadei L, Brunetti N, et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr. 2005;82(3):636-43.
14. Hooshmand B, Solomon A, Kåreholt I, Leiviskä J, Rusanen M, Ahtiluoto S, et al. Homocysteine and holotranscobalamin and the risk of Alzheimer disease: a longitudinal study. Neurology. 2010;75(16):1408-14.
15. Obeid R, Herrmann W. Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia. FEBS Lett. 2006;580(13):2994-3005.
16. Kalmijn S, Launer LJ, Lindemans J, Bots ML, Hofman A, Breteler MMB. Total Homocysteine and Cognitive Decline in a Community-based Sample of Elderly Subjects: The Rotterdam Study. Am J Epidemiol. 1999;150(3):283-9.
17. Arioğul S, Cankurtaran M, Dağli N, Khalil M, Yavuz B. Vitamin B12, folate, homocysteine and dementia: are they really related? Arch Gerontol Geriatr. 2005;40(2):139-46.
18. Chen S, Honda T, Ohara T, Hata J, Hirakawa Y, Yoshida D, et al. Serum homocysteine and risk of dementia in Japan. J Neurol Neurosurg Psychiatry. 2020;91(5):540-6.
19. Xu W-H. Large artery: an important target for cerebral small vessel diseases. Ann Transl Med. 2014;2(8):78.
20. Kalaria RN. Small Vessel Disease and Alzheimer's Dementia: Pathological Considerations. Cerebrovasc Dis. 2002;13(2):48-52.
21. Moretti R, Caruso P. The Controversial Role of Homocysteine in Neurology: From Labs to Clinical Practice. Int J Mol Sci. 2019;20(1).
22. Gunstad J, Bausserman L, Paul RH, Tate DF, Hoth K, Poppas A, et al. C-reactive protein, but not homocysteine, is related to cognitive dysfunction in older adults with cardiovascular disease. J Clin Neurosci Off J Neurosurg Soc Australas. 2006;13(5):540-6.
23. Li Y, Wang L, Zhang W, Fang Y, Niu X. No association between elevated homocysteine levels and carotid atherosclerosis in a rural population in China. Stroke Vasc Neurol. 2016;1(4):154-60.
24. Potter K, Hankey GJ, Green DJ, Eikelboom J, Jamrozik K, Arnolda LF. The effect of long-term homocysteine-lowering on carotid intima-media thickness and flow-mediated vasodilation in stroke patients: a randomized controlled trial and meta-analysis. BMC Cardiovasc Disord. 2008;8:24.
25. S Z, Bp M, P B, Pg K, C M, R W, et al. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: a multicenter, randomized, controlled trial. J Am Coll Cardiol. 2006;47(6).
26. Sundström J, Sullivan L, D'Agostino RB, Jacques PF, Selhub J, Rosenberg IH, et al. Plasma Homocysteine, Hypertension Incidence, and Blood Pressure Tracking. Hypertension. 2003;42(6):1100-5.
27. Sadeghian S, Fallahi F, Salarifar M, Davoodi G, Mahmoodian M, Fallah N, et al. Homocysteine, vitamin B12 and folate levels in premature coronary artery disease. BMC Cardiovasc Disord. 2006;6(1):38.

28. Raina SK, Chahal JS, Kaur N. Correlation between homocysteine and Vitamin B12 levels: A post-hoc analysis from North-West India. Int J Health Allied Sci. 2015;4(2):115.
29. Takenoshita S, Terada S, Yoshida H, Yamaguchi M, Yabe M, Imai N, et al. Validation of Addenbrooke's cognitive examination III for detecting mild cognitive impairment and dementia in Japan. BMC Geriatr. 2019;19.
30. Quental NBM, Brucki SMD, Bueno OFA. Visuospatial function in early Alzheimer's disease--the use of the Visual Object and Space Perception (VOSP) battery. PloS One. 2013;8(7):e68398.
31. Jiang Y, Wang Y, Yuan Z, Xu K, Zhang K, Zhu Z, et al. Total Cerebral Small Vessel Disease Burden Is Related to Worse Performance on the Mini-Mental State Examination and Incident Dementia: A Prospective 5-Year Follow-Up. J Alzheimers Dis. 2019;69(1):253-62.
32. Yilmaz P, Ikram MK, Niessen WJ, Ikram MA, Vernooij MW. Practical Small Vessel Disease Score Relates to Stroke, Dementia, and Death. Stroke. 2018;49(12):2857-65.
33. Rensma SP, van Sloten TT, Launer LJ, Stehouwer CDA. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2018;90:164-73.
34. McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A Controlled Trial of Homocysteine Lowering and Cognitive Performance. N Engl J Med. 2006;354(26):2764-72.
35. Kwok T, Lee J, Law CB, Pan PC, Yung CY, Choi KC, et al. A randomized placebo controlled trial of homocysteine lowering to reduce cognitive decline in older demented people. Clin Nutr. 2011;30(3):297-302.
36. Ford AH, Almeida OP. Effect of homocysteine lowering treatment on cognitive function: a systematic review and meta-analysis of randomized controlled trials. J Alzheimers Dis JAD. 2012;29(1):133-49.
37. Oijen M van, Jong FJ de, Witteman JCM, Hofman A, Koudstaal PJ, Breteler MMB. Atherosclerosis and risk for dementia. Ann Neurol. 2007;61(5):403-10.
38. Mathiesen EB, Waterloo K, Joakimsen O, Bakke SJ, Jacobsen EA, Bønaa KH. Reduced neuropsychological test performance in asymptomatic carotid stenosis: The Tromsø Study. Neurology. 2004;62(5):695-701.
39. Wang X, Jackson DC, Mitchell CC, Varghese T, Wilbrand SM, Rocque BG, et al. Classification of Symptomatic and Asymptomatic Patients with and without Cognitive Decline using Non-invasive Carotid Plaque Strain Indices as Biomarkers. Ultrasound Med Biol. 2016;42(4):909-18.

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