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COGNITIVE IMPAIRMENT IN HYPERTENSIVES

Natasha Tipnis[1], Girish Rajadhyaksha[1], Meghav Shah[2]

Correspondence: *meghav87@yahoo.co.in*
[1]Department of Medicine, Topiwala National Medical College and B.Y.L. Nair Charitable Hospital, Mumbai, Maharashtra, India
[2]Department of Cardiology, Topiwala National Medical College and B.Y.L. Nair Charitable Hospital, Mumbai, Maharashtra, India

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ABSTRACT

Background: Hypertension and dementia increase parallel to age.
Objective: The purpose of this study was to study the effect of hypertension on cognition before age-related cognitive impairment begins to set in.
Methods: In this prospective, cross-sectional study conducted at a tertiary-care centre between May 2014 and December 2015, 300 (150 hypertensives and 150 normotensives) participants were compared. Patients were divided into groups according to age, gender, education, and duration of hypertension. The Hindi Mini-Mental State Examination (HMMSE) was used to detect cognitive impairment.
Results: Overall, occurrence of cognitive impairment was 53 (35.3%) in hypertensives and 37 (24.7%) in normotensives. Below 60 years male and female hypertensives and normotensives had comparable mean HMMSE scores, although not statistically significant. Sixty years and above male and female normotensives achieved slightly higher HMMSE scores than male and female hypertensives, however this finding was statistically significant ($p=0.002$) for males ≥60 years. Among the cognitive domains, orientation to time ($p=0.009$), registration ($p=0.018$), recall ($p=0.031$), and 3 step command ($p=0.014$) were statistically different between hypertensives and normotensives. Periventricular white matter ischemia was discovered in 8 (5.3%) and 2 (1.3%) hypertensives and normotensives, respectively.
Conclusion: Although hypertension was not statistically associated with cognitive decline in hypertensives <60 years, hypertensives >60 years showed statistical significance with cognitive decline. Furthermore, specific cognitive domains such as orientation to time, registration, recall, and 3 step command displayed statistical significance for cognitive decline. Future prospective, large-scale studies are warranted to investigate these and other possible associations.

Keywords: Age, cognitive impairment, dementia, Hindi mini-mental state exam, hypertension

Introduction

Dementia is a leading cause of cognitive impairment in the geriatric population. The burden of dementia tends to increase exponentially with age, prevailing at a rate of 65% in the population above 65 years.[1-3] It is one of the most debilitating neurological disorders, characterized by memory impairment affecting at least one intellectual function of the brain severe enough to hinder daily activities and restrict independence.[2] The incessant epidemic of dementia together with lack of preventive or curative treatment has revived interest in studying the modifiable risk factors of dementia.

Hypertension is one such modifiable risk factor displaying a robust association with cognitive impairment, as well as coronary artery disease, cerebrovascular accidents, chronic kidney disease and retinopathy. Blood pressure also increases parallel to age eliciting high prevalence of hypertension in the elderly population. This risk factor is predictive of dementia and has thus been implemented as a risk-score for prediction of dementia.[4]

Earlier studies assessing the correlation between blood pressure and cognitive impairment have yielded controversially discrepant results. Positive, negative, U-shaped, J-shaped, and even no correlations have been found between blood pressure and cognition from cross-sectional and longitudinal studies. Furthermore, some studies have concluded higher rates of association with elevated blood pressure whilst others have concluded the same with low blood pressure.[2,5,6] Indeed, the association between blood pressure and cognitive decline is a complex beast as asserted by Sabayan and Westendorp in their invited commentary.[7]

Even among physicians in India, there is a lack of awareness regarding the role of hypertension in cognitive impairment. This is reflected by the scarcity of Indian studies on the same and the absence of cognitive assessment in standard protocols for work up of hypertension and related complications. Thus, this study was designed to determine the occurrence of cognitive impairment in hypertensives and normotensives according to age, gender, level of education, risk factors, and duration of hypertension. Increased education level is associated with better and preserved cognition. Thus, to remove the bias of level of education on cognitive impairment, we assessed the level of cognitive impairment in patients of hypertension based on their educational qualifications. To explore a potential relationship between duration of hypertension and cognitive impairment as well as for statistical purposes, patients were categorized according to duration of hypertension. Secondary aims of the study were to assess (i) whether hypertension affects various domains of cognition differently (ii) magnetic resonance imaging (MRI) changes in patients with cognitive impairment, and (iii) correlations between cognitive impairment and other end-organ damages in hypertensives.

Methods & Materials

Study design and patient population

This was a prospective, cross-sectional study conducted at a tertiary-care centre in India, conducted from May 2014 to December 2015. A total of 300 (150 cases and 150 controls) patients participated in the study as shown in Figure 1. The inclusion criteria for cases was hypertensive participants above the age of 40 years, whereas the inclusion criteria for controls was normotensive participants above the age of 40 years. The exclusion criteria for all participants was pre-diagnosis of dementia secondary to other causes. Participants were grouped according to age (<60 and ≥60 years), gender, education level (uneducated, grade 1–7, grade 8–12, and graduate) and duration of hypertension (5–10, 11–20, and >21 years). The study protocol was approved by the local Ethics Committee prior to commencement of the study. All patients provided written informed consent.

Hindi Mini-Mental State Examination

Cognitive function was assessed with the Hindi Mini-Mental State Examination (HMMSE). The HMMSE is a 30-point scale for assessing cognitive function. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. It was established by merging the globally adopted Mini-Mental State Examination (MMSE) developed by Folstein et al.[8] and the Hindi Mental State Examination developed by Ganguli et al.[9] as detailed in their paper. Among the cultural, educational and socio-economic diverse participants in our study, many were elderly and belonged to an illiterate and rural background. Therefore, we decided to implement the HMMSE as a screening tool in our study. The HMMSE was developed to counter bias in India among rural and illiterate elders as it remains uninfluenced by education and culture fair as compared with the MMSE. A cut-off score of 27 was used to detect mild cognitive impairment and a score of 23 to detect dementia.

Statistical analysis

The sample size was calculated with reference to a previous study.[10] The prevalence of cognitive impairment in general population has been taken as 40% and that in a normal population as 18%. An α-error of 5% and a β-error of 20% have been taken. Normally distributed continuous variables were expressed as mean ± standard deviation and were compared using student t-test. Non-uniformly distributed continuous variables were expressed as median (range) and compared with Mann-Whitney U test. Categorical variables were expressed as number (percentage) and were compared using chi-square test. A p value of <0.05 was considered statistically significant. All statistical analysis was done using Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program, version 15.

Data collection and medical information

Demographic characteristics including age, sex, education level, and cardiovascular risk factors such as hypertension, diabetes mellitus, smoking, alcoholism, tobacco use, ischemic heart disease (IHD), and stroke/transient ischemic attack (TIA) were obtained from patient case report forms. Laboratory investigations included renal function tests and urine albumin tests. Electrocardiography and 2D echocardiography were performed for all participants. MRI was performed for participants with HMMSE <23 if advised by the neurologist. Fundus examination for retinopathy was also performed.

Results

Demographics of study population

Hypertensives and normotensives were well matched for age, weight, smoking, alcoholism, and IHD. However, there were significant differences between the two groups with regards to gender, height, body mass index (BMI), education level, tobacco use, and stroke/TIA. Demographics of the study population are demonstrated in Table 1.

Table 1: Demographics of the study population

Variable	Hypertensive (n=150)	Normotensive (n=150)	p value
Age, years	60 (40–85)	59 (40–83)	0.680
Male, n	80 (53.3%)	101 (67.3%)	0.013
Weight, kg	63 (35–95)	60 (148–180)	0.458 †
Height, cm	158 (140–199)	164.5 (40–99)	<0.001 †
BMI, kg/m^2	24 (14–37)	23 (14–37)	<0.007 †
Education			
Uneducated	47 (31.3%)	54 (36.0%)	0.007
1–7 grade	60 (40.0%)	47 (31.3%)	
8–12 grade	33 (22.0%)	42 (28.0%)	
Graduate	10 (6.7%)	7 (4.7%)	
Risk Factors			
Smoking	25 (16.7%)	35 (23.3%)	0.149
Alcoholism	23 (15.3%)	26 (17.3%)	0.639
Tobacco use	23 (15.3%)	42 (28.0%)	0.008
IHD	24 (16.0%)	23 (15.3%)	0.874
Stroke/TIA	13 (8.7%)	4 (2.7%)	0.025

All data are expressed as median (min – max) or as number (%). †Mann–Whitney test. IHD-ischemic heart disease; TIA-transient ischemic attack

Association of age and cognitive impairment in hypertensives and normotensives

In hypertensives <60 years, 19 (35.9%) participants had cognitive impairment whereas, 55 (56.7%) did not have cognitive impairment. However, in hypertensives ≥60 years, 34 (64.1%) had cognitive impairment whereas, 42 (43.3%) did not have cognitive impairment. This association was statistically significant (p=0.015). In normotensives <60 years, 18 (48.6%) had cognitive impairment whereas 58 (51.3%) did not have cognitive impairment. In normotensives ≥60 years, 19 (51.4%) had cognitive impairment whereas 55 (48.7%) did not have cognitive impairment. However, this association was not statistically significant. Association of age group and cognitive impairment in hypertensives and normotensives is illustrated in Figure 2.

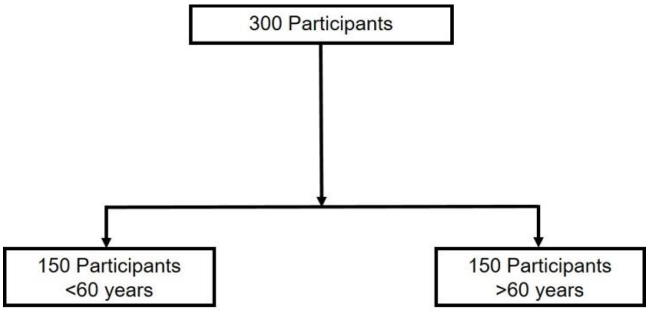

Figure 1. Study Flow

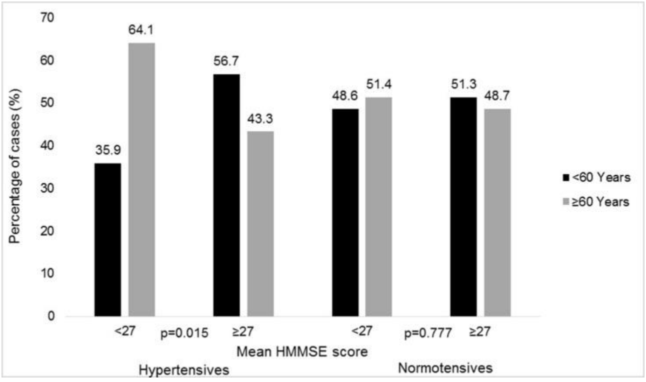

Figure 2. Association of age group and cognitive impairment in hypertensives and normotensives

Table 2. Association of age group, gender, education, risk factors and mean HMMSE score between hypertensives and normotensives

Variables	Mean HMMSE score		
	Hypertensive (n=150)	Normotensive (n=150)	p value
HMMSE			
HMMSE score	27 (15–30)	28 (21–30)	0.003 †
Score <27	53 (35.3%)	37 (24.7%)	0.044
Score ≥27	97 (64.7%)	113 (75.3%)	
Age			
<60 years	26.33±2.57 (n=74)	27.84±2.20 (n=76)	0.242 †
≥60 years	26.12±4.15 (n=76)	27.35±2.16 (n=74)	0.022 †
Gender			
Males <60 years	27.41±2.27 (n=48)	27.92±1.62 (n=37)	0.428 †
Females <60 years	27.24±2.37 (n=37)	27.71±2.21 (n=28)	0.386 †
Males ≥60 years	26.35±2.57 (n=43)	27.68±2.20 (n=53)	0.002 †
Females ≥60 years	25.82±4.15 (n=33)	26.52±2.16 (n=21)	0.858 †
Education			
Uneducated	25.64±3.30 (n=47)	26.91±2.10 (n=54)	0.087 †
1–7 grade	26.82±2.97 (n=60)	27.49±2.22 (n=47)	0.316 †
8–12 grade	27.76±2.06 (n=33)	28.55±1.43 (n=42)	0.092 †
Graduate	27.70±1.49 (n=10)	28.00±1.83 (n=07)	0.601 †
Risk factors			
Smoking	26.32±2.95 (n=25)	27.60±2.05 (n=35)	0.019 †
No smoking	26.79±2.93(n=125)	27.60±2.07(n=115)	0.064 †
Alcoholism	26.13±3.12 (n=23)	27.85±1.78(n=26)	0.018 †
No alcoholism	26.82±2.89 (n=25)	27.55±2.11(n=35)	0.081 †
Tobacco use	26.22±3.57 (n=23)	28.02±1.77 (n=42)	0.035 †
No tobacco use	26.80±2.80(n=127)	27.44±2.14(n=108)	0.129 †
IHD	26.21±3.49 (n=24)	26.39±2.55(n=23)	0.872 †
No IHD	26.81±2.81(n=126)	27.82±1.88(n=127)	0.005 †
Stroke/TIA	25.23±4.59(n=13)	27.00±4.08(n=04)	0.412 †
No stroke/TIA	26.85±2.70(n=137)	27.62±2.00(n=146)	0.026 †

All data are expressed as mean (SD) or number (%). †Mann–Whitney test. HMMSE-Hindi mini-mental status examination; IHD-ischemic heart disease; TIA-transient ischemic attack.

Table 3. Association of hypertensive retinopathy, urine albumin, 2D echocardiography, and mean HMMSE score among hypertensives

Variable	Mean HMMSE score	p value
Hypertensive retinopathy (n=33)	24.55±3.76	0.001
No Hypertensive retinopathy (n=117)	27.32±2.32	
Urine albumin(n=42)	26.14±3.62	0.193
No urine albumin(n=108)	26.94±2.60	
2D Echo (HHD/DD)(n=62)	25.73±3.48	0.001
No2D Echo (HHD/DD)(n=88)	27.41±2.24	
Duration of hypertension		
5– 10 years (n=120)	26.89±2.91	0.105
11–20 years (n=29)	25.90±2.94	
>21 years (n=1)	29.00±0.00	

All data are expressed as mean (SD). HMMSE-Hindi mini-mental status examination; HHD-hypertensive heart isease; DD-diastolic dysfunction

Table 4. Comparison of mean HMMSE score according to cognitive domains between hypertensives and normotensives

Variable	Mean HMMSE score		
	Hypertensive (n=150)	Normotensive (n=150)	p value
Orientation to time (5)	5 (2–5)	5 (2–5)	0.009 †
Orientation to place (5)	5 (3–5)	5 (3–5)	0.352 †
Registration (3)	3 (0–3)	3 (2–3)	0.018 †
Concentration (5)	5 (0–5)	5 (0–5)	0.226 †
Recall (3)	1 (0–3)	2 (0-3)	0.031 †
Visual recognition (2)	2 (2–2)	2 (2–2)	1.000 †
Proverb (1)	1 (0–1)	1 (1–1)	0.317 †
Imitate (1)	1 (0–1)	1 (0–1)	0.562 †
3 Step command (1)	1 (0–1)	1 (0–1)	0.014 †
Sentence formation (1)	1 (0–1)	1 (0–1)	1.000 †
Drawing (3)	3 (0–3)	3 (0–3)	0.377 †

All data are expressed as median (min – max). †Mann–Whitney test. HMMSE-Hindi mini-mental status examination

Table 5. MRI investigational findings

Variable	Hypertensive (n=150)	Normotensive (n=150)	p value
Magnetic Resonance Imaging			
Periventricular white matter ischemia	8 (5.3%)	2 (1.3%)	0.029
Lacunar infarcts	11 (7.3%)	3 (2.0%)	
Corticocerebral atrophy(CCA)	06 (4.0%)	1 (0.7%)	

All data are expressed as number (percentage).

Association of age, education level, risk factors, and mean HMMSE score between hypertensives and normotensives

Overall, 53 (35.3%) hypertensives and 37 (24.7%) normotensives attained a mean HMMSE score <27 and were therefore cognitively impaired. Below 60 years male and female hypertensives and normotensives had comparable mean HMMSE scores, although not statistically significant. Sixty years and above male and female normotensives achieved slightly higher HMMSE scores than male and female hypertensives, however this finding was statistically significant (p=0.002) for males ≥60 years. Normotensives achieved slightly greater mean HMMSE scores for all education levels, but only 8–12 grade education was statistically significant (p=0.092). Risk factors, smoking (p=0.019), alcoholism (p=0.018), tobacco use (p=0.035), no IHD (p=0.005), and no stroke/TIA (p=0.026), had comparable mean HMMSE scores of statistical significance for hypertensives and normotensives. Association of age, education level, risk factors, and mean HMMSE score between hypertensives and normotensives are detailed in Table 2.

Association of hypertensive retinopathy, urine albumin, 2D echocardiography, and mean HMMSE score among hypertensives

Hypertensive retinopathy and no hypertensive retinopathy (p=0.001) and 2D echocardiography and no 2D echocardiography (p=0.001) both displayed a statistically significant association. The association of hypertensive retinopathy, urine albumin, 2D echocardiography, and mean HMMSE score among hypertensives is given in Table 3.

Comparison of mean HMMSE score according to cognitive domains between hypertensives and normotensives

Among the cognitive domains, orientation to time (p=0.009), registration (p=0.018), recall (p=0.031), and 3 step command (p=0.014) were statistically different between hypertensives and normotensives. Mean HMMSE scores for hypertensives and normotensives according to cognitive domains is demonstrated in Table 4.

MRI investigational findings

Periventricular white matter ischemia was discovered in 8 (5.3%) and 2 (1.3%) hypertensives and normotensives, respectively. The MRI findings are detailed in Table 5.

Discussion

Researchers have postulated long-standing hypertension with onset from midlife plays a positive role in the progression of late-life cognitive impairment and dementia.[2,4,11,12] However, several studies investigating the association between hypertension and cognition have included participants above the age of 60 years.[2-5,10,13-15] It is against this background that we attempted to study the effect of hypertension on cognition before age-related cognitive impairment begins to set in. The study, therefore included participants aged 40 years and above. High prevalence of hypertension within the country along with increasing diagnoses of hypertension in individuals in their thirties and forties have also prompted this study.

The present study aimed to study occurrence of cognitive impairment in hypertensives and normotensives according to age, gender and education level. Literature derived from prior studies have estimated rates of mild cognitive impairment or related disorders ranging from 0.5–36%.[14] In line with this, our study reported 53 (35.3%) and 37 (24.7%) cognitive impairment in hypertensives and normotensives, respectively. Similarly, Sharifi et al.[2] reported 63.9% and 61.0% cognitive impairment in hypertensives and normotensives, respectively. Singh et al.[14] reported 19.3% mild cognitive impairment in their study population. These results confirm a positive association between hypertension and cognitive decline as found in several other studies. The broad spectrum of prevalence rates may be justifiable by varying diagnostic criteria and participant demographics.

Studies on the impact of sociodemographic characteristics on cognitive performance in elderly populations have revealed associations between age, gender, and education with cognition.[14,16,17] Devraj et al.[13] showed a progressive decline in performance on all domains of cognitive function in both sexes as age advanced. Earlier studies have hinted at gender variability whilst assessing cognitive performance. Our study shows that <60 years, hypertensive and non-hypertensive males and females performed similarly, achieving comparable mean HMMSE scores. However, ≥60 years, males outperformed females in both hypertensive and non-hypertensive subjects. This finding is consistent with studies that have reported males to outperform normotensive female subjects and consider female gender as a risk factor for cognitive impairment.[17] However, in hypertensives, males had higher mean HMMSE scores than females, although not statistically significant. This finding highlights the probable role of hypertension as a risk factor for dementia which equalizes the gender specific advantage.

The hallmark HYVET study[4] demonstrated the significant effect of lower education on cognitive impairment. The authors asserted that less educated populations were more prone to develop incident dementia. In line with these findings, our study documented lower HMMSE scores for less educated participants as compared to higher educated participants regardless of hypertensive status. These results correlate with findings of Dufouil et al.[18] in which higher educated patients achieved higher MMSE scores than lower educated patients across all categories of mild, moderate and severe graded white matter hyperintensities. Similarly, Devraj et al.[13] and Muela et al.[16] also reported influence of education on cognitive function. These findings evidence the independent association of education with cognition, irrespective of hypertensive status. Furthermore, these observations support study methodology of Sharifi et al.[2] and Muela et al.[16] in which the MMSE cut-off points were calculated in accordance with level of education.

Long duration or uncontrolled hypertension has been considered a powerful predictor of poor cognitive outcome.[10] Muela et al.[16] reported 7.0%, 9.0%, and 14.0% cognitive impairment in normotensives, stage 1, and stage 2 hypertension, respectively. They also reported mean scores of (28.0±2.0, 27.4±2.1, 26.8±2.1, p=0.001) and (25.5±3.2, 24.9±2.8, and 23.4±3.7, p=0.004) for normotension, stage 1 and 2 hypertension on the MMSE and Montreal Cognitive Assessment scales, respectively. These findings evidence increased cognitive impairment corresponding with severity of hypertension. However, our results do not support this observation. Our results may be explained by the decreased tendency of elderly patients with hypertension to develop cognitive impairment and dementia. This may be explained by the hypothesis of cognitive reserve which asserts that older individuals with greater experiential resources exhibit better cognitive functioning and are able to tolerate higher levels of brain pathology before displaying clinical symptoms.[19]

Various risk factors have been implicated in playing a role in the increased risk of dementia. The landmark Framingham Heart Study[20] revealed independent and cumulative effects of obesity on cognition. Singh et al.[14] indicated chronic smoking and diabetes to be associated with greater risk for cognitive impairment. Knopman et al.[11] reported greater cognitive impairment with diabetics on both the digital symbol subtest (DSS) and first-letter word fluency (WF) tests. Sharifi et al.[2] have concluded high diastolic blood pressure may be a risk factor for cognitive impairment in the elderly.

The progressive and irreversible nature of dementia sheds light on the importance of identification and primary prevention of risk factors. Therefore, regardless of other underlying etiologies, controlling blood pressure as a pharmacologically modifiable risk factor might prevent dementia or delay the progression of cognitive decline.

Limitations

Some limitations of the current study deserve mention. Firstly, it was not possible to perform MRI brain examinations on all the participants due to financial constraints. These examinations were performed only on participants with HMMSE score <23. If MRI brain examinations were performed on all participants, a better insight into the MRI changes in cognitive impairment would have been provided. Secondly, although the MMSE is a good screening test for detecting cognitive impairment, it is not a very sensitive or very specific test. Thirdly, this was a cross-sectional study, imparting limited information in the form of a one-time cognitive assessment of the subjects. Longitudinal studies with a larger sample size and repeated cognitive assessments of subjects using other cognitive tests in addition to MMSE over a period of many years will be able to give better information about the effect of risk factors such as hypertension, diabetes and IHD on cognition. Lastly, participants in this study were on multiple drugs, in varying doses and for varying periods of time. Hence, it was not possible to study the association of the drugs with cognitive impairment. Longitudinal studies, monitoring the cognition of participants on drug therapy over the years will be able to define the effects of various drugs on cognition.

Conclusion

Although hypertension was not statistically associated with cognitive decline in hypertensives <60 years, hypertensives >60 years showed statistical significance with cognitive decline. Furthermore, specific cognitive domains such as orientation to time, registration, recall, and 3 step command displayed statistical significance for cognitive decline. Future prospective, large-scale studies are warranted to investigate these and other possible associations.

Acknowledgement

None.

Conflict of Interest

The authors report no conflicts of interest.

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