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Original Research Article

Brain MRI: a useful tool for screening of hypertensive patients for silent cerebro-vascular damage

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ABSTRACT

Background: Worldwide hypertension is an important public-health challenge because of its high frequency and concomitant risks of cardiovascular, renal, cerebrovascular disease and death. Current guidelines for the management of hypertension mainly recommend the search for preclinical damage to the heart and kidneys. However, extending this search to other organs, for instance the brain, might improve risk stratification, might optimize antihypertensive therapy and might, in the end help to further reduce the burden of disease attributable to hypertension.
Methods: 84 consecutive hypertensive patients with no target organ damage were enrolled in study to find out silent brain damage over a period of one year.
Results: Mean body mass index (BMI) of the study population was 28.4±2.5 kg/m^2 (range 23.2 to 35.3kg/m^2). 33 (39.3%) subjects had white matter lesions. 13 (15.47%) study subjects were found to have vascular changes which included micro angiopathic changes, infarcts and reduced/slow blood flow. 33 (39.3%) subjects were found to have normal brain MRI in the study. Early brain MRI was found to be beneficial in patients who had uncontrolled blood pressure either due to lack of treatment or irregular use of anti-hypertensive treatment. This was true for every age group in general and particularly in subjects above the age of 50 years.
Conclusions: The screening of hypertensive patients for silent cerebrovascular damage with brain MRI may be useful in stratifying the risk of future cerebrovascular disease.

Keywords: Brain, End organ damage, Hypertension, MRI

INTRODUCTION

According to the World Health Organization (WHO), hypertension is estimated to cause over seven million premature deaths and 4.5% of the total disease burdens worldwide, its impact being higher than that of tobacco use and alcohol consumption.

Data from the WHO also indicate that about 62% of cerebro-vascular disease and 49% of ischemic heart disease are attributable to non-optimal blood pressure (BP) levels.[1,2]

Hypertension is the most prevalent and best modifiable vascular risk factor for cardio- and cerebrovascular disease in general. Besides reduction in BP, the main purpose of anti-hypertensive treatment is to prevent the concomitant cardiovascular, cerebro-vascular and renal complications, to extend longevity, and to improve quality of life.[3]

Hypertension causes structural and functional alterations in the vasculature in general and in target organs such as the heart, kidneys and brain in particular.[4,5] Although initially these changes are compensatory in nature, they will invariably lead to compromised organ function in patients with untreated or uncontrolled hypertension. Importantly, once organ involvement has developed, cardio-vascular prognosis worsens. Moreover, the presence of target-organ damage may also determine the choice for a specific drug or drug combination in the treatment of hypertension.[6]

Current guidelines for the management of hypertension mainly recommend the search for pre-clinical cardiac and renal damage, i.e., detection of left ventricular hypertrophy (LVH) and micro-albuminuria or impaired renal function, respectively.[7,8]

Both conditions have been associated with an increased incidence of cardiovascular complications.[9,10] Thus one may question whether the detection of pre-clinical cardiac and renal damage sufficiently covers the risk associated with hypertension, or leaves a significant number of high-risk patients unnoticed, e.g., because silent damage to other organs such as the brain remains undetected.

Hypertension guidelines only recognize symptomatic stroke or transient ischemic attack (TIA) as markers of established hypertensive organ damage of the brain.[6,7] Stroke has been associated with a high rate of disability, coexisting morbidity and a high risk of death.[10,11] Thus it is important to estimate or predictthe risk of future stroke. To this end, risk scores, based on the presence of common cardiovascular risk factors including the level of BP, have been developed. With the advent of magnetic resonance imaging (MRI), it has become possible to detect cerebro-vascular disease already in a preclinical phase.[12,13]

Silent cerebro-vascular disease harbours prognostic relevance, reporting a two to five times higher risk of future stroke in the presence of silent ischemic brain damage.[14-16] The brain is an early target of organ damage due to high blood pressure, which is the major modifiable risk factor for stroke and small vessel disease. Stroke is the second leading cause of death and the number one cause of disability worldwide and over 80% of strokes occur in the elderly.

Despite this, hypertension guidelines do not yet recommend the assessment of pre-clinical cerebro-vascular disease to estimate the risk of stroke, next to and in the same way as for instance the presence of LVH is recommended in cardiovascular risk stratification.[6,7]

There is strong evidence that cerebral white matter lesions in hypertensive patients should be considered a silent early marker of brain damage.

The mechanisms leading to silent cerebro-vascular damage are complex and not well understood. Partly, this results from the heterogeneous presentation of brain lesions, which can be present as extensive lesions of chronic ischemia, small, mostly deep infarcts, or small bleedings. Nevertheless, all these changes appear to be caused by a shared, generalized cerebral small-vessel disease (SVD). Hypertension leads to both functional and structural (adaptive as well as degenerative) changes in the cerebral microvasculature. A variety of small-vessel pathologies have been observed in the hypertensive brain.[17]

Functionally, hypertension impairs cerebro-vascular auto-regulation, which, in general, compensates for decreases in total cerebral blood flow (CBF) to keep brain perfusion pressure constant.[18]

By definition, silent cerebro-vascular disease occurs in the absence of stroke like symptoms. The most frequently reported manifestations of silent cerebro-vascular damage on MRI associated with hypertension are white matter hyper-intensities (WMHs), silent brain infarcts (SBIs), and brain micro-bleeds (BMBs).[19-21]

METHODS

An observational cross-sectional study in patients of hypertension aged between 18-60 years was conducted in the Medicine department of a teaching Hospital of a Medical College after taking Prior approval of the Institutional Ethical committee.

All hypertensive patients with BP ≥140/90 mmHg were enrolled in the study. Patients who had target organ damage like cerebro-vascular accident, myocardial infarction and chronic kidney disease were excluded. Patients who suffered from co-morbid conditions like diabetes mellitus, with history of drug abuse/dependence of narcotics and sedatives, had history of psychiatric illness, epilepsy and head injury etc. which may have led to brain atrophy were excluded from the study.

On baseline all participants enrolled in the study were subjected to a pretested and semi-structured questionnaire regarding socio demographic profile, relevant history (both past and present) along with the duration of hypertension, treatment taken (if any) and compliance. General physical examination and systemic examination was conducted, blood pressure was measured twice and recorded relevant investigations including chest radiograph, eye examination of fundus, micro-albuminuria and echocardiography, MRI were recorded.

Statistical analysis

Data was performed with SPSS student version 20.0 (SPSS Inc. Chicago, USA). Descriptive statistics, frequency percentages were determined for categorical

variables. Odds ratio (OR) and 95% confidence interval (95% CI) were calculated for categorical variables.

Chi square or Fischer exact test (as appropriate) were applied as tests of association. A p value of <0.05 was considered as statistically significant.

RESULTS

A total of 84 patients presenting to Medicine Outpatient Department during study period with blood pressure 140 mmHg systolic and 90 mmHg diastolic and above (both newly diagnosed or on treatment) but with no target organ damage were enrolled for the current study. 54 (64.3%) males and 30 (35.7%) were female. Mean age of the study subjects was 40.3±10.8 years with range of 19 to 60 years. 45 (53.6%) patients belonged to rural areas and 39 (46.4%) to urban areas.

Headache was the most common presenting symptom present in 60 (71.4%) patients followed by giddiness in 10 (12%) of the patients. Maximum number of patients presented after duration of 1-6 months of start of symptoms. Mean body mass index (BMI) of the study population was 28.4±2.5Kg/m^2 (range 23.2 to 35.3 kg/m^2). 53 (63.1%) of the participants were overweight (BMI= 25-29.9 Kg/m^2) and 21 (25%) were obese (>30Kg/m^2). 42 (50%) of study participants were current smokers and 32 (38.1%) were current alcohol consumers.

In the study population, maximum subjects had systolic blood pressure in the range of 140-149 mm of Hg i.e. 61 (72.6%) subjects followed by 18 (21.4%) patients in range of 150-159mm of Hg and finally 5 (6%) patients in the range of ≥160mm of Hg. Maximum subjects had diastolic blood pressure in the range of 90-99mm of Hg i.e.78 (92.8%) subjects followed by 6 (7.2%) patients in the range of ≥100mm of Hg. Regarding treatment seeking behaviour, 10 (11.9%) subjects were on regular anti-hypertensive treatment, 15 (17.9%) subjects were consuming anti-hypertensive medicine irregularly, 7 (8.3%) were on anxiolytic drugs, 15 (17.9%) subjects were on proton pump inhibitors (PPI)/non-steroidal anti-inflammatory drugs (NSAIDs)/other drugs and 37 (44.1%) were not on any treatment at the time of enrolment in the study.

Specific MRI findings

All the 84 patients were subjected to MRI of brain. 33 (39.3%) subjects had normal MRI study out of which 20 (23.8%) were male and 13 (15.5%) were female.

White matter lesions (WML) were found in 33 (39.3%) of the study population, constituting of 8.3% of brain atrophy, 4.8% of lacunar infarcts, 16.7% of non-specific hyper intensities and 9.5% of other WML including small cystic foci, gliotic changes, old infarcts and altered signal intensities. Microangiopathy was seen in 10 (11.9%) subjects. Other findings seen were micro bleeds, reduced cerebellar blood flow and multiple infarcts and slow flow in left jugular vein. The total vascular changes were found in 13 (15.5%) cases which mainly included microangiopathic changes, infarcts and reduced/slow blood flow.

There was a higher odd of hypertension related brain damage of the patients with increasing age, more so for patients more than 50 years old. With increase in duration of hypertension, the odds of having brain damage increased (Table 1).

Table 1: Relationship of study variables with brain changes on MRI.

Variable	parameter	MRI changes		Odds ratio (C.I.)	P-value*
		Brain changes	No changes		
Age	18-29	10	9	1**	0.57
	30-39	12	10	1.08	
	40-49	14	11	1.15	
	50-60	15	3	4.5	
Sex	Male	34	20	1.3 (0.5-3.2)	
	Female	17	13		
Duration of hypertension	1day- 1week	4	5	1**	0.92
	1week-1month	14	3	5.83	
	1month - 5.9 months	19	16	1.48	
	6 months- 1 years	6	5	1.5	
	>1 year	8	4	2.5	

*p<0.05 is considered statistically significant**Reference category

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It was seen that regular anti-hypertensive treatment had significant protective effect with odds of 0.23 (0.05-0.97) with subjects being less prone to damage their brain as compared to hypertensive patients who were not on anti-hypertensives or non- compliant to anti- hypertensive treatment ($p<0.04$). The patients with systolic BP i.e. 150-159 mm Hg were having odds ratio of 2.06 and with systolic BP≥160mm Hg had odds ratio 3.18 suggesting higher odds of brain damage with increasing systolic BP.

The study subjects with diastolic BP (≥100mmHg) were having higher odds of brain damage identified on MRI but the relationship was not statistically significant (Table 2).

Table 2: Relationship of clinical presentations with brain damage on MRI.

Variable	parameter	MRI changes		Odds ratio (CI)	P-value*
		Brain changes	No changes		
Symptoms	headache	37	21	1.5 (0.6-3.9)	0.39
	Others	14	12		
Systolic blood pressure (mm Hg)	140-149	34	27	1**	0.18
	150-159	13	5	2.06	
	≥160	4	1	3.18	
Diastolic blood pressure (mm Hg)	≥100	04	02	1.3 (0.23- 7.6)	0.79
	90-99	47	31		
Treatment	Regular anti-Hypertensives	3	7	0.2 (0.05- 1)	0.04
	Irregular or no Anti-Hypertensives	48	26		

*p<0.05 is considered statistically significant**Reference category

DISCUSSION

The current study enrolled 84 hypertensive patients with mean age 40.3±10.8 years (range of 19 to 60 years) in one-year study duration. Most of the earlier studies have seen effects of age and vascular risk factors on brain injury in elderly individuals. Previous studies of individuals aged 60 years or older suggest that, even in people with well controlled hypertension, increased systolic blood pressure is associated with clinically silent brain injuries such as increased brain atrophy, grey-matter atrophy, white-matter injury including white-matter hyper intensities (WMH), and clinically asymptomatic infarcts.[22,23] In this study, has been done in younger age group (18-60 years old) to justify the usage of MRI Brain in hypertensive patients as an early and definitive predictor of brain damage. A similar age group as compared to this study had been included in the Framingham Heart Study where 579 subjects were enrolled in the third-generation cohort (mean age 39·2 years, SD 8·4) who underwent brain MRI between June 2009 and June 2010.[24]

It was evident form this study that the effects of high blood pressure in the brain are evident as early as fourth to fifth decade of life. The Framingham Heart Study had similar observations where the mean age of the study population with significant post hypertension brain lesions was in the fifth decade.[24] De Carli C et al also concluded that such changes appear in early middle age with a higher prevalence in the fifth decade of life.[25] Debette S et al also said that early changes in brain appear in the middle ages with significant prognostic value for cognitive deterioration in later years of life.[26]

In this study, suggests that subjects who were on regular anti-hypertensive treatment were less at risk for brain damages when compared to those who were not on any anti-hypertensive treatment or irregular or were non-compliant ($p<0.04$). Similar conclusions were also made by A. L. Vlek et al, C. Dufouil et al, in their respective studies cerebrovascular events.[27,28] The risk of WMHs is even higher in patients with untreated and poorly controlled hypertension.[29,30]

Results from this study, study indicate that Hypertension is associated with injury to white-matter microstructure, regional grey matter and microvasculature in healthy adults. White matter lesions (WML) were found in 33 (39.29%) of the study population in the present study. In hypertensive cohorts, in consonance with the current study, the reported frequencies of WMHs ranged between 12% and 55%.[31,32]

Previous work from the Framingham Heart Study and other studies of elderly individuals have identified cross-sectional and longitudinal associations between midlife vascular risk factors, brain atrophy, WMH, and cognitive ability late in life.[33-36] In this study extends these findings even in young adult ages, with preferential susceptibility to specific anterior white-matter tracts and grey-matter regions even before evidence of increased WMH

volumes. There are findings that suggest that correct antihypertensive treatment could efficiently slow WML progression. Strong evidence suggests that cerebral WML in hypertensive patients should be considered a silent early marker of brain damage

Evidence of even subtle brain injury at young ages should affect how physicians think about hypertension diagnosis and treatment. These data strongly suggest that substantial brain injury could precede clinically manifest disease, indicating that prevention of stroke or cognitive impairment due to hypertensive vascular disease might require treatment at younger ages than presently thought.[36]

This study also suggests certain relevant indicators which justify the usage of MRI Brain in hypertensive patients as an early and definitive predictor of brain damage even in those patients who show no target organ damage like retinopathy, nephropathy or any significant echocardiographic changes. Early MRI Brain particularly was clearly found to be beneficial in patients who had uncontrolled blood pressure due to lack of treatment or those who were on irregular anti-hypertensive treatment. This is true for every age group in general and patients above 50 years in particular.

Further once these early and significant changes are seen, the patient should be encouraged to adopt a healthier life style, motivated to avoid smoking and alcohol consumption and to take regular treatment as advised by the treating physician and regular follow up visits to prevent the late sequel of these early changes like stroke and other target organ damages.

In this study, also justifies the growing trend among the medical fraternity of early diagnosis of hypertension with immediate initiation of treatment, to prevent the late complications which manifest years after the preclinical stage of hypertension. Initially the patient is asymptomatic with no target organ damage but the seed of the complications which come years later are already sown by the time the patient gets concerned about his or her hypertension and already the damage that is done by this time becomes irreversible. This is where the role of non-invasive diagnostic techniques like MRI where by establishing a link between the findings present and its predictive value in accessing the possible complications come into play. The correlation can help us in understanding the importance of early detection and treatment of hypertension to help an individual lead a healthy and fruitful life. Therefore, screening of hypertensive patients for silent cerebrovascular damage with brain MRI, besides assessing cardiac and renal damage, may be useful in stratifying the risk of future cardio- and cerebrovascular disease.

Further longitudinal studies are needed to investigate whether duration of increased BP has cumulative effects on white-matter integrity in young adults. These will also help to assess the rate of further stroke/transient ischemic attack, other cardiovascular events and their predictors. Despite these limitations, the public health implications of these results are clear.

Authors have found that support the benefits of non-invasive techniques like MRI in detecting the morbidities due to raised blood pressure at an early stage and provide possible cure sooner than later.

CONCLUSION

The screening of hypertensive patients for silent cerebrovascular damage with brain MRI may be useful in stratifying the risk of future cerebrovascular disease.

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