ORIGINAL ARTICLE

The Effect of Hypertension and Diabetes Mellitus on White Matter Changes in MRI Brain: A Comparative Study between Patients with Alzheimer's Disease and an Age-matched Control Group

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Abstract

Background: White matter hyperintensities (WMH) on MRI brain in the periventricular and deep white matter regions are commonly seen in older persons with normal cognition and in patients with AD.

Aims: To compare presence and severity of WMHs in patients with AD with that in a cognitively normal control group, and to evaluate effect of presence of Hypertension and Diabetes on WMHs in both groups.

Material and Methods: Thirty four patients with AD were serially recruited from Neurology and Psychiatry OPDs. An age and gender matched cohort of 24 persons with MMSE over 27/30 from the community acted as controls. Vascular risk factors, MMSE and MRI brain were assessed in all. Fezeka's and Pasquier grading of WMH and atrophy were done. Periventricular WMHs (PVWMH) and Deep WMH (DWMH) were assessed separately.

Results and Conclusions: Overall, Periventricular WMHs of grade 2 and over were seen in 19/34 patients, and in 7/24 controls (P value 0.044). Significantly higher grades of PVWMHs were seen in hypertensives as compared to non-hypertensives in the case group, and in women compared to men. In the control group, hypertension had no effect on severity of PVWMHs. Among both Diabetics and non-diabetics, no difference in PVWMHs was found between the case and control groups.

DWMHs were, conversely, seen only in the control group.

Overall, over a quarter of cognitively normal older persons had WM hyperintensities of grade 2 and over on MRI brain; 55% of AD patients had PVWMH of Gd 2 or over, and no DWMHs.

Background

The diagnosis of Alzheimer's disease (AD) does not require that the MRI brain should be free of old ischemic insults. If a patient presents with the classical features of memory loss progressing to a more general cognitive dysfunction, any minor ischemic changes on the MRI may be considered irrelevant except in the rare instance of dominant hippocampal infarcts. In the Indian population, subclinical lacunas and periventricular /deep white matter changes on the MRI are often picked up incidentally due to high prevalence of uncontrolled or undiagnosed vascular risk factors.[1,2] The co-incident occurrence of these changes in a patient with AD possibly raises the concern of a diagnosis of mixed dementia and also impacts progression of severity of Dementia.[3,4] This study is designed to see the effect of hypertension and diabetes mellitus on white matter changes in MRI brain of patients with AD, as compared to an age matched, cognitively normal control group.

Materials and Methods

This prospective observational comparative study was performed between known patients of Alzheimer's diseases (AD) and healthy individuals (control) over 60 years of age. The patients of AD were diagnosed as per DSM-4 criteria, and recruited from Neurology and Psychiatry OPDs in a tertiary care public hospital over 11 months. Patients with prior recorded and clinically obvious strokes were excluded. For the control group, we included age and gender matched persons from the community with MMSE score over 27/30, who consented to participate in the study, and who had not had a previous clinical stroke.

All subjects underwent evaluation for vascular risk factors, viz., Hypertension and Diabetes Mellitus. Review of case records, BP recordings twice, and review of fasting and post prandial blood sugars and HbA_{1C} levels, along with treatment details were noted, before concluding that subjects had either Hypertension or Diabetes. Current MMSE scores, and duration of illness were noted for the patient group.

MRI protocol included 3D flair sag, T2 axial, SWI axial, Diffusion axial, and T1 3D sequences.

Features noted included Fazeka's score grades 0-3 in periventricular as well as Deep white matter,[5] and grading of cerebral atrophy by Pasquier scale in the range of 0-4.[6] Additionally, presence of any lacunes, gliosis, or micro hemorrhages (on GRE sequence) were noted. The films were independently read by 2 senior radiologists.

Our primary outcome measure was the evaluation of White matter hyperintensities in Periventricular and Deep white matter areas (PVWMH and DWMH) on MRI. The secondary

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Table 1: Demographic variables, prevalence of diabetes, hypertension and MMSE scores in AD and control groups

Variables		AD (34)	Control (24)
Gender	Male	26 (76%)	16 (66%)
	Female	8 (24%)	8 (34%)
Age groups	Mean ± SD	72 ± 6.36	67 ±5.12
	< 65	2	7
	65 - 69	9	11
	70 - 74	10	3
	75 - 79	9	2
	>80	4	1
Hypertensive/Normotensive		16/18	12/12
Diabetics/Non-Diabetics		11/23	6/18
MMSE Score	<= 15	5	>27
	16 - 20	22	
	>= 21	7	

Table 2: Correlation of vascular risk factors with MRI Imaging features in AD and control groups

Study Parameter - Groups 0 – 1		Periventricular WMH fazeka score				Deep white matter score				Cerebral atrophy pasquier scale			
		2-3	χ 2	p Value	0 – 1	2-3	χ 2	p Value	0 - 1	2-3	χ 2	p Value	
Non-HTN	*AD*	11	7	0.625	0.429	18	0	5.000	0.025	10	8	7.273	0.007
	Control	9	3			9	3			12	0		
HTN	*AD*	4	12	4.861	0.027	16	0	4.480	0.034	6	10	11.667	0.001
	Control	8	4			9	3			12	0		
Non-diabetics	*AD*	12	11	1.706	0.192	23	0	5.664	0.017	10	13	14.898	0.000
	Control	13	5			14	4			18	0		
Diabetics	*AD*	3	8	2.487	0.115	11	0	4.156	0.041	6	5	3.864	0.049
	Control	4	2			4	2			6	0		
Male	*AD*	14	12	0.913	0.339	26	0	7.184	0.007	13	13	11.586	0.001
	Control	11	5			12	4			16	0		
Female	*AD*	1	7	6.394	0.012	8	0	2.286	0.131	3	5	7.273	0.007
	Control	6	2			6	2			8	0		

variables to main explanatory variable noted, were gender, presence of Hypertension and Diabetes Mellitus.

The study was cleared by the institutional ethics committee.

Data was analyzed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) for Windows and Microsoft Excel version 2010. Descriptive analysis for numerical variables were shown by mean ± SD. Frequencies for categorical data were expressed in percentage. Fisher's exact ($\chi 2$) test was used to test the statistical significant difference among the AD and control groups. P values less than 5% were considered significant.

Results

58 subjects were evaluated in this study, 34 being patients with Alzheimer's disease (79 % male) and 24 being age and gender matched controls with normal cognition as per MMSE. Overall median age of all the participants was 69 years. Median age in control group was 66 years, and in the AD group was 72 years (Table 1).

Duration of AD was 2 to 8 years. Majority of patients had AD for 2 to 4 years (34/38- 89.4%). Average MMSE for those with disease under 2 years was 19.3, whereas with disease duration more than 6 years, it was 15. In the AD group, 16 (42%) subjects were hypertensive and 11 (29%) were diabetics, while in control group 12(50%) were hypertensive and 6 (25%) were diabetics (Table 1). The prevalence of these comorbid conditions was statistically similar in the 2 study groups. In our study, both the duration and control of Diabetes and Hypertension were comparable in the AD and control groups. (Duration of Diabetes in control vs AD was 13.6 vs 14 yrs, and of Hypertension was 14.7 vs 16 yrs. Mean fasting sugar in control vs AD was 112 vs 140 mg%, and PLBS was 178 vs 192 mg%, whereas average BP was 154/90 mm Hg in control group and 150/90 mm Hg in AD group).

Overall, PVWMHs of grade 2 and over were significantly more prevalent in AD group (seen in 19/34 AD patients, and in 7/24 controls -P value 0.044). Among Hypertensives, significantly more subjects had worse PVWMHs of grade 2 and 3 in the AD group, than in the control group, as opposed to non-hypertensives where no such difference was found (Table 1). Among both Diabetics and non-diabetics, no difference in severity of PVWMHs was found between the AD and control groups. Among women, the AD group had significantly higher number of persons in the worse category of PVWMHs (Grade 2 and 3), than the control group. This was not seen among males (Table 2).

With regard to DWMHs, none in the patient group had Grade 2 or over changes, whereas 6/18 in the control group had Grade 2 or over changes (P value 0.002). Thus, significantly higher number of subjects were seen in worse category of DWMS, in the control group as compared to the AD group, in hypertensives as well as non-hypertensives, and in diabetics as well as non-diabetics.

No participants from control group had a cerebral atrophy score of 2 or more, while AD group had 18 (53%) with cerebral atrophy score of 2 or more. Due to this, cerebral atrophy score was significantly higher in AD group for the comorbid conditions.

Discussion

The presence of WM changes in patients with AD, with or without existing vascular risk factors such as Hypertension and DM, raises the concern of a diagnosis of mixed dementia, as well as adding a burden of subcortical Dementia (executive function abnormality) to the existing cortical dementia in AD. It is well recognized that vascular risk factors are common to the pathogenesis of both VaD and A.D.[7–9] Subcortical vascular changes on MRI are usually gradual and progressive and not related to a particular index stroke. Their prevalence in AD patients, and possible contribution to cognitive dysfunction, was the subject of interest in this study.

The high prevalence of recognized as well as undiagnosed Hypertension and Diabetes in the general population in India has been documented in various population studies.[1,2] We looked at the prevalence of Hypertension and Diabetes among our 2 study groups and evaluated the effect of these 2 variables on WMHs on MRI. These comorbid conditions were statistically similar in the 2 study groups.

In our study, among the 34 patients with AD, 15 had 0-1 Fazeka's scores and 19 had Gd 2-3, in the PVWM, as compared to17 and 7 with Gd 0-1, and 2-3 respectively, in the control group. This difference for higher grades of score in the AD group was significant (p 0.047, OR 0.32. 95% C I 0.107-0.9868). Conversely, when the DWM was considered, none of the patients with AD had the higher grades of Fazeka's

score, all 34 patients having only 0-1 grades; in the control group, however, 6/24 subjects had Gd 2-3 changes. This difference for higher grades of the score in the control group was again significant at a P value of 0.033(OR 24.24, 95%C I 1.29-454.6).

Clinicopathological and imaging correlations of the WM hyperintensities have been described.[10,11] The available pathology describes periventricular WMH as having discontinuous ependyma, gliosis, loosening of the white matter fibers, and myelin loss around tortuous venules in perivascular spaces. The gliosis, demyelination, and fiber loss have been reported to worsen as the periventricular WMH worsens.[12] In deep WMH, there was demyelination, gliosis, and axonal loss around perivascular spaces, with vacuolation and increased tissue loss as the lesions became more severe. The periventricular and Deep WM changes have been described as a continuum.[12–14] Various studies have also shown correlation of WMH with vascular risk factors,[15] and shown progression in severity with aging and cognitive decline over time.[16,17]

In our study, severity of PVWMHs was more marked in AD group, whereas severity of DWMHs was more in the control group. This calls into question the etiopathogenesis, links with vascular risk factors, and association with cognitive dysfunction, of PVWMHs and DWMHs, as separate entities. Studies have looked at the difference between periventricular and Deep WM hyperintensities, ascribing different etiopathogenesis to each. Smooth PVWMHs may be due to interstitial fluid leakage in periventricular area and are likely to be non-ischemic, whereas DWMHs and irregular PVWMHs have been postulated to be ischemic in etiology. Additionally, DWMHs are likely to be due to small vessel disease whereas irregular PVWMHs may result from chronic hemodynamic insufficiency.[18–20] The higher prevalence of deep WMHs in the control group as compared to the AD group could be due to higher prevalence of undocumented risk factors such as proximal carotid stenosis or higher lipid levels, in the control group.

In the control group with normal cognition, 7/24 (29.1%) and 6/24 (25%) subjects had higher grades of Fazeka's scores in PVWM and DWM respectively. Half of the control population had Hypertension, and a quarter were Diabetic. Additional vascular risk factors which were operational were gender and age. Alcohol and tobacco abuse, high waist hip ratio, and lipid abnormalities could also have been contributory, but were not recorded in this study. In this control group, the presence of Hypertension did not influence development of worse DWMHs, as ¼ of the control group had Grade 2-3 DWMH in both the hypertensive and the non-hypertensive groups. Also, in the control group, the presence of Diabetes did not affect development of worse grade of DWMH (2/9 with Gd 2 or over in non- DM group as compared to 1/3 in Diabetic group- P 0.173, 95% C I -38.64-71.57). Similarly, 1/3rd of both genders had Grade 2-3 DWMC.

The correlation of WM abnormalities on MRI with aging and vascular risk factors on the one hand, and with progression of cognitive abnormalities on the other, is the subject of many ongoing studies. Medina et al have demonstrated significant decrease in white matter integrity in the posterior and deep white matter regions, on DTI-MRI studies, in AD and Mild Cognitive impairment.[21] Akisaki et al have demonstrated correlation between WMH and lower cognition in an elderly, diabetic Japanese population.[22]

The dichotomy between PVWMHs and DWMHs in our study, was of particular interest. Previous studies appear to suggest that DWMHs are more representative of true ischemic insults, than PVWMHs. Our study suggests that DWMHs are largely prevalent in an older, cognitively normal population, and not specifically associated with AD. It is possible that these MRI changes of WMHs would also correlate with severity and duration of AD; due to paucity of numbers, we did not subanalyse for WMH grading in relation with AD severity. Another limitation of our study was lack of volumetric analysis. Volumetric analysis of the hyperintensities would help to quantitate the data, and better correlations with changes in cognitive scores over time would then be possible. Despite these limitations, we believe the study's findings are applicable and generalisable to the Indian population.

Conclusion

This study showed that over a quarter of cognitively normal, older Indian persons had WM hyperintensities of grade 2 and over on MRI brain.

Fifty five percent of patients with AD had PVWMHs of Gd 2 or over on MRI, significantly more than in an age-matched control group. PVWM hyperintensities were significantly more in the hypertensive AD group, as compared to the non-hypertensive AD group. DWMH were, conversely, seen only in the control group, but their severity did not show an association with gender, or the presence of Hypertension and Diabetes.

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