AGE RELATED WHITE MATTER LESIONS ON MAGNETIC RESONANCE IMAGING

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ABSTRACT

Objective: *To find out the frequency of cerebral white matter lesions (WML) in elderly individuals with no neurological symptoms.*

Methodology: *This descriptive study was carried out at Radiology Department, Military Hospital, Rawalpindi; January to December 2003. One hundred asymptomatic patients of either gender, aged 50 years and more without a known systemic disease were selected and divided into two groups of age 50-65 years and more than 65 years and MRI brain was performed. WML when found were classified as subcortical and periventricular hyperintensities and rated for both hemispheres simultaneously along with regional distribution of the WML. Frequency of each type of WML was assessed in the sample. Relationship with age and gender of patients was also sought.*

Results: *Subcortical WML were present in 54% (n=54) of subjects. Periventricular WML were found in 19% (n=19) of study population. Both subcortical and periventricular WML were more frequently observed in more than 65 years age group. However findings were not statistically significant (p-values = 0.8333 & 0.3646 respectively). Periventricular white matter lesions were observed more commonly in males with statistically significant distribution (p-value = 0.0018). Subcortical WML were also more frequently observed in males. However the distribution was statistically insignificant (p-value =0.1566). Distribution of subcortical WML was most frequent in frontal lobes (62.9%) followed by parieto-occipital regions (33.3%).*

Conclusion: *WML are a frequent finding on MRI brain of asymptomatic elderly individuals of either gender with periventricular WML having a statistically significant preponderance in males.*

Keywords*: Brain, aging. Magnetic Resonance Imaging. White matter Lesion (WML).*

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INTRODUCTION

Cerebral white matter lesions (WML) are focal areas of abnormal increased signal intensity on T_2 weighted, Fluid Attenuation Inversion Recovery (FLAIR) and proton density (PD) magnetic resonance (MR) images in the cerebral white matter and appear hyperintense as compared to the surrounding white matter. Such lesions are found in cerebral white matter in many disease processes with deficient or abnormal myelination including multiple sclerosis, many metabolic and some inflammatory disorders. WML are also found on MR imaging of brain in elderly individuals in association with other pathologic conditions including silent stroke and hypertension[1, 2].

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Cerebral WML have been significantly associated with age[3-5] and therefore such lesions have also been designated as "Age Related White Matter Changes" (ARWMC)[6]. These lesions have even been considered as an index for assessing age-related cerebral health with promising results[7]. Cerebral WML may not be considered benign because they have been associated with cognitive impairment in demented patients[8] as well as in healthy elderly individuals[9, 10].

The advent of MRI has focused attention on white matter lesions. Changes in cerebral white matter, detectable with increasing frequency by MRI, are associated with aging and conceivably may contribute to the development of specific cognitive deficits. The reported frequency of age related WML varies widely. This is likely to be due to a number of differences between studies,

including selection of study population, technical aspects of imaging and methods of image analysis.

Our study was designed to assess the frequency of WML in asymptomatic, elderly Pakistani subjects keeping in view the limited availability of MRI based data regarding age related cerebral WML in such individuals.

METHODOLOGY

The study was carried out at the department of Radiology, Military Hospital Rawalpindi from January 2003 to December 2003 using a 1.5 Tesla MRI machine Magneton Symphony Version Syngo MR 2002A by Seimens.

A total of 100 patients of either gender with age 50 or above and with no neurological symptoms or a systemic disease were randomly selected by convenience non-probability sampling method from a pool of patients coming for MRI of regions other than brain. Patients with age less than 50 years and those with neurological symptoms, personal history of hypertension, diabetes mellitus, intracranial tumor, malignancy or white matter disease were excluded. Informed consent was taken before inclusion in study.

Using standard protocols, plain scanning was done in coronal and axial planes. Sagittal scans were done if required. Scanning criteria included: Number of slices, 12 for each plane; Bandwidth, variable receiver bandwidth was used for first (10.67kHz) and second (4.27KHz) echo; Slice thickness, 6 mm with interslice gap of 20%; Pulse sequences, axial T1, T2, PD and Turbo FLAIR and coronal turbo FLAIR; Pulse parameters, T1 (TR: 485ms, TE: 14ms), T2 (TR: 2236, TE: 90ms), PD (TR: 2236ms, TE: 20ms); FOV, 230; Total scan time, approximately 20 minutes.

Rating of WML was done using rating scale developed at "Department of clinical neuroscience and Department of Radiology, Karolinska Institute at Haddinge University Hospital, Sweden" [6]. White matter lesions were defined as ill-defined hyperintensities ≥5 mm on both T2 and PD/FLAIR images. These lesions were classified into those in the subcortical and periventricular region. Well-defined areas of size 2-5 mm with signal characteristics the same as cerebrospinal fluid were labeled as Lacunes. If lesions with these characteristics were ≤2 mm, they were considered perivascular spaces.

Subcortical WML were rated as 0): No lesion. 1): Focal lesions. 2): Beginning confluence of lesions 3): Diffuse involvement of the entire region. Following brain areas were used for rating: Frontal lobes (frontal lobe anterior to central sulcus), parieto-occipital regions (parietal and occipital lobes together), temporal lobes (border between temporal lobes was approximated as line drawn from posterior part of sylvian fissure to trigone areas of the lateral ventricles) and infratentorial regions (including brainstem and cerebellum). Rating was done for both hemispheres simultaneously. The overall grading of subcortical WML was calculated by adding up the scores for the four regions (range 0-12).

Periventricular WML were also rated as per region: Adjacent to frontal horns (frontal capping), Adjacent to lateral wall of lateral ventricles (bands), Adjacent to occipital horn (occipital capping). Scoring was done on a scale of 0): No white matter lesions. 1): Pencil thin periventricular lining. 2): Smooth halo or thick periventricular lining. 3): Large confluent white matter lesions. This was done for both hemispheres simultaneously. The overall grading of periventricular white matter lesions were calculated by adding up the scores for the three regions (range 0-9).

All ratings were performed at one occasion by two qualified raters who had at least one year experience of MR reporting (HU, SA) independently and later on a consensus was reached. Raters were blinded from knowing the age and gender of the individuals.

All data was processed in SPSS version 10 for statistical analysis. Mean and standard deviation (SD) was calculated for age. Frequencies (percentages) were calculated for age, gender and site of lesion. Chi square test was used to compare the frequency of lesions with reference to site and gender between the two age groups. A p-value of less than 0.05 was considered significant.

RESULTS

A total of 100 subjects (67 males and 33 females) participated in the study. 50-65 years age group had 74 while more than 65 years age group had 26 subjects. The mean age of the subjects was 62 years (SD: 8.89 months) with age ranging from 50–89 years. Subcortical WML were common being present in 54% (n=54) of subjects. Periventricular WML (Figure A) were found in 19% (n=19) of study population (Table 1).

The participant response rate was 74% and only 26% for the younger and older age groups respectively.

Subcortical WML were more frequently seen in the >65 years age group (57.7%) as compared to 50-65 years age group (52.7%). Periventricular WML were even more common in

>65 years age group being present in 26.9% as compared to 16.2% in 50-65 years age group though the overall frequency of periventricular WML was less as compared to that of subcortical WML(Table 1). The association between increasing age and white matter lesions of either type was not statistically significant in our study (p-values = 0.8333 & 0.3646 respectively).

Forty out of 67 males (59.7%) and 14 out of 33 females (42.4%) had subcortical WML. Thus WML in subcortical regions were more frequently seen in males with no statistical significance (p-value = 0.1566). The difference was more marked in case of periventricular WML where 19 males (28.3%) were affected as compared to no female. This was statistically significant (p-value = 0.0018) (Table 2).

Table 2 illustrates that 46% subjects were completely free of subcortical WML. 5% of the subjects (4 males and 1 female) had diffuse involvement of an entire subcortical region. 81% of subjects including all females had no periventricular WML (Table 2). Out of three types of periventricular lesions, thin periventricular lining was more commonly seen.

Out of 54 subjects having subcortical WML 34 (63%) had their frontal lobes affected (Table 3). The next more commonly affected region was parieto-occipital regions (n=16; 29.6%).

Table 1: Distribution of WML according to Age (*n*=100)

Age group	Subcortical WML (Grades)		Periventricular WML (Grades)	
	No Lesion (0)	Lesions (1-3)*	No Lesion (0)	Lesions (1-3)*
50-65 years (n=74)	35	39 (52.7%)	62	12 (16.2%)
>65 years (n=26)	11	15 (57.7%)	19	7 (26.9%)
Total (n=100)	46	54 (54%)	81	19 (19%)
	p- value = 0.8333		p- value = 0.3646	

Key: *Subcortical WML: 0): No lesion. 1): Focal lesions. 2): Beginning confluence of lesions 3): Diffuse involvement of the entire region. Periventricular WML: 0): No white matter lesions. 1): Pencil thin periventricular lining. 2): Smooth halo or thick periventricular lining. 3): Large confluent white matter lesions.*

Table 2: Distribution of WML according to Gender and Grades: (*n*=100)

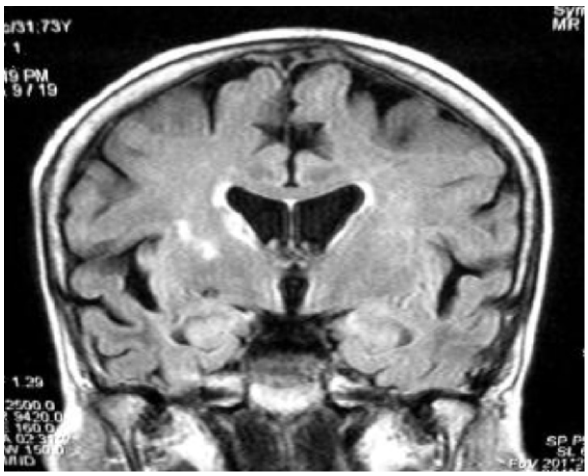
Gender	Subcortical WML (Grades)					Periventricular WML (Grades)				
	0	1	2	3	Total (1-3) *	0	1	2	3	Total (1-3) *
Males (n=67)	27	25	11	4	40 (59.7%)	48	14	4	1	19 (28.3%)
Females(n=33)	19	10	3	1	14 (42.4%)	33	0	0	0	0 (0%)
Total (n=100)	46	35	14	5	54 (54%)	81	14	4	1	19 (19%)
	p- value = 0.1566					*p- value = 0.0018*				

Key: *Subcortical WML: 0): No lesion. 1): Focal lesions. 2): Beginning confluence of lesions 3): Diffuse involvement of the entire region. Periventricular WML: 0): No white matter lesions. 1): Pencil thin periventricular lining. 2): Smooth halo or thick periventricular lining. 3): Large confluent white matter lesions*

Table 3: Regional distribution of WML

	Frequency		Percentage
No lesions	46		(*n*=46; 46%)
Frontal lobes	34	(63%)	(*n*=54; 54%)
Parieto-occipital lobes	16	(29.6%)	
Temporal lobes	3	(5.6%)	
Infratentorial region	1	(1.8%)	
Total	100		

Figure A: Coronal FLAIR MR image of an elderly asymptomatic subject showing periventricular hyperintensities



Annex 'A' Indications For MRI

S. No	Region	Number of Individuals
1	Cervical spine	31
2	Lumbar spine	29
3	Knee joint	16
4	Thoraco- Lumbar spine	7
5	Hip Joint	6
6	Thoracic spine	6
7	Elbow Joint	2
8	Para-nasal sinuses	3

Annex 'B' Rating Scale for white Matter Lesions

Subcortical WML	
0	No lesions
1	Focal lesions
2	Beginning confluence of lesions
3	Diffuse involvement of the entire region
Periventricular WML	
0	No white matter lesions
1	Pencil thin periventricular lining
2	Smooth halo or thick periventricular lining
3	Large confluent white matter lesions

DISCUSSION

Our study shows that the severity of subcortical and periventricular WML is dependant on age and sex. In our study, WML were in particular seen more frequently in more than 65 years age group. There was a slight rise in the frequency of cerebral WML with increasing age as compared to 50-65 years age group though it was not statistically significant. This finding suggests that age plays an important role in the development of cerebral WML apart from many other factors.

We found WML of both varieties to be more common in men as compared to women. The difference was especially marked in periventricular WML which were entirely absent in females in our study population.

Subcortical WML were most frequently seen in frontal lobes, followed by parieto-occipital regions. Infratentorial WML were rarely seen. These findings correspond with Scheltens et al who found in a study of 24 normal elderly subjects (mean age of 68 years) that severity of WML was highest in frontal lobe[10]. Although frontal and parietal lobes are larger than occipital and temporal lobes, this difference cannot explain the vast difference in WML. We are not aware of any difference in vascularization between lobes that might explain the large interlobe difference in frequency of WML.

The strength of the study is its large number of asymptomatic elderly subjects. This has helped in evaluation of the WML, suggesting that in the absence of neurological symptoms, alteration in subcortical and periventricular white matter may represent the predominant neuro-anatomic changes in normal aging. Another important feature is the distinction between WML in subcortical and periventricular regions. This allows us to evaluate whether WML in these two regions have a different pathogenic background and different clinical correlates.

Some shortcomings in methodology need to be considered. A reasonable attempt was made to make the study sample representing the general population by excluding those having any neurological symptoms or any known systemic disease though ideally the individuals should have been randomly chosen from the general population instead of those coming for MRI examination for any problem.

Our study had a response rate of 74% in participants aged 50-65 years decreasing to 26% in participants aged more than 65 years. The resultant selection bias, especially in the oldest age category, could not be avoided because of the limited availability of individuals for the study. We consider it likely that same was the case in male female response (frequency of WML in elderly females has been underestimated).

Another point for concern is the possible misclassification in WML rating scale. Although anatomical landmarks were chosen to separate the lobes, we cannot exclude the possibility that some misclassification occurred. When subcortical and periventricular WML are abundantly present, it may sometimes become difficult to distinguish between the two. However, the presence of two competent raters with initial individual rating, later on reaching a consensus helped reduce this problem in our study.

The age-related increase in WML found is consistent with previous reports based on MRI based studies. It is now generally accepted that frequency of age related WML increases with aging. These changes in the “optimally healthy” aging brain are different from those seen in primary age related diseases such as Alzheimer's disease[11]. As a result of high sensitivity of T_2 weighted spin echo sequences and specialized FLAIR sequence MR images reveal high signal foci within the white matter. Estimate of the incidence of these hyperintensities in the brain of healthy, elderly individuals have ranged from 30-90%[9,12]. Gerard and Weiseberg found subcortical lesions in only 10% of patients older than 60 years. According to this study, to a certain extent, the presence of these hyperintensities limits the sensitivity of MR for white matter disease, as these are often normal variants or related to deep cerebral ischaemia, but they can be mistaken for or can obscure more serious pathology[13]. Some authors also report that increased brachial pulse pressure is age-independently associated with WMLs in asymptomatic elderly individuals[14].

Our study shows a higher frequency of subcortical lesions (57.7%) in more than 65 years age group with no statistical significance (p-value$\leq$1).

CONCLUSION

Our study shows that the presence of WML on MR scans of elderly individuals is a frequent finding affecting almost 54% of otherwise healthy individuals. The chance of finding WML increases with age. Males are rather more frequently affected than females with periventricular WML having a statistically significant preponderance in males.

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None Declared

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CONTRIBUTORS

HU conceived the idea and planned the study. SA did the data collection and analyzed the study. Both the authors contributed significantly to the research that resulted in the submitted manuscript.