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Original Article

Radiology Section

Essence of ADC Values in Leukoaraiosis Imaging and Association of Leukoaraiosis with Cognitive Dysfunction

SIVAKAMI RATHINAM, RAGINI SINGH

ABSTRACT

Introduction: Leukoaraiosis is a common cerebral white matter disease identified radiologically as discrete focal or diffuse patchy bilateral hypodense on computed tomography and hyperintense on T2 weighted Resonance Imaging. Underlying pathogenesis and clinical essence of this radiological finding is yet to be defined clearly. Some patients present with impairment of cognition and dementia.

Aim: To assess the usefulness of ADC values in grading the leukoaraiosis and defining its complete extent, identification of the normal appearing white matter with early demyelination changes which is not detectable on conventional MRI and to evaluate the association of leukoaraiosis with impaired cognition.

Materials and Methods: This prospective study was done at MRI unit of Department of Radiodiagnosis, C.S.M. Medical University, Lucknow, India during a period of one year from August 2007 to July 2008. Study comprised of Group 1 (cases, n-60) with leukoaraiosis and Group 2 (controls, n-20), healthy subjects with no leukoaraiosis both above 50 years of age. All subjects were studied with 1.5T MRI machine, ADCav values of leukoaraiosis lesions and normal white matter (WM) were estimated.

Results: The ADCav values of the leukoaraiotic regions were higher than the normal white matter and the values proportionately increased with the grade of the lesions (p-value $\leq$ 0.001). The ADCav values of normal white matter were higher in cases than controls and the values increased with grade of leukoaraiosis (p-value < 0.001). Significant association found between reduced Mini Mental Status Examination (MMSE) and presence of leukoaraiosis (p-value $\leq$ 0.001) and proportional reduction of MMSE score with increasing grade of leukoaraiosis (p-value $\leq$ 0.001).

Conclusions: Increasing ADC values of leukoaraiosis lesions with increasing grade could be used as a grading scale of leukoaraiosis. Higher ADCav values of normal white matter in patients with leukoaraiosis which were increasing with higher grades of leukoaraiosis, is probably representing those areas that are prone to develop leukoaraiosis over time and hence help in assessment of complete extent of the lesion. The significant association of leukoaraiosis with impaired cognition, proposes leukoaraiosis as one of the cause for cognitive function.

Keywords: ADC map, Dementia, Ischaemic demyelination, Normal white matter

INTRODUCTION

Leukoaraiosis is a synonym of ischaemic demyelination. It is a common cerebral white matter disease identified radiologically as discrete focal or diffuse patchy bilateral hypodense on computed tomography (CT) and hyperintense lesions on T2 Weighted (T2WIs) Magnetic Resonance Imaging (MRI)[1,2]. The prevalence of leukoaraiosis is found to be high in people older than 65 years [2,3]. Many studies have demonstrated the significant association of leukoaraiosis and many form of cerebro-vascular disease suggesting the possibility of ischemia as the cause for this disease entity [4]. However, the underlying pathogenesis and clinical essence of this radiological finding is yet to be defined clearly [2].

Some people are asymptomatic and others present with impairment of cognition [5,6], disturbed gait [4], disorders of mood disorders and dementia[7-9]. Leukoaraiosis adds to the overall morbidity and mortality of the patients and precipitates the stroke risk [9,10].

Apart from CT and conventional MRI, leukoaraiosis can also be imaged with Diffusion Weighted Imaging (DWI) and can be assessed with Apparent Diffusion Coefficient (ADC) values. Advantage of MRI over CT is that reveals those lesions which are difficult to identify on CT. However, the white matter that appears normal on T2W MRIs can also have early demyelination changes, obscuring the exact extent of the lesion. The usefulness of ADC values in overcoming this

shortcomings of conventional MRI and the association of leukoaraiosis and cognitive impairment are evaluated in this study.

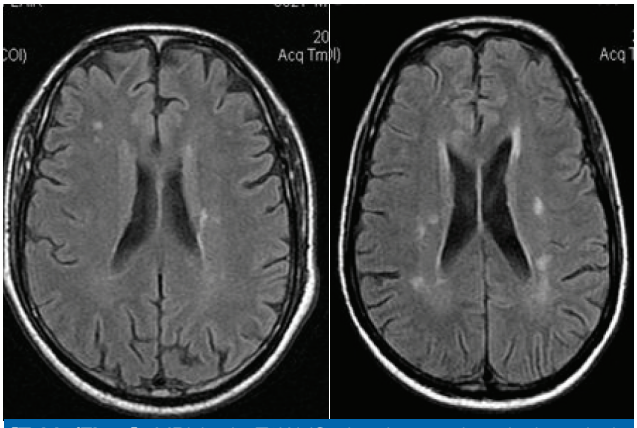
MATERIALS AND METHODS

This was a single blinded prospective study done at MRI unit of Department of Radiodiagnosis, C.S.M. Medical University, Lucknow, India, during a period of one year from August 2007 to July 2008. Ethical committee clearance was acquired for the study. Consent was taken from all the subjects who were included in the study. The radiologists evaluating the MRI were blinded for the clinical data of the patient. The study comprised two groups of subjects all above 50 years:

Group 1- with total of 60 subjects with leukoaraiosis; Group 2- with total of 20 healthy subjects with no Leukoaraiosis and no nervous system disease. Precise age and sex matching of these control subjects with cases was not possible. The patients having multifocal white matter hyperintensities other than leukoaraiosis, moderate to severe hydrocephalus with peri-ventricular CSF leak were excluded from the study.

Imaging Technique

All the subjects underwent conventional T1,T2, FLAIR weighted MRI on Signa Excite 1.5 T Gemsow (GE) MR Scanner. In addition DWI sequence was performed with a echo-planar imaging (EPI) following parameters TR 4038 ms, TE 125 ms, 22 slices of 5mm thickness, interslice gap of 1mm, field of view 230×230 mm^2, and matrix size $152×10^5$ interpolated to 256×256. Measurement of Diffusion was done in 3(x, y, and z) orthogonal directions with b values of 0 and 1000 s/mm^2. ADCav maps were created using spin echo T2 EPI sequences. The calculations of ADCav values in the regions of leukoaraiosis and normal appearing white matter in bilateral frontal and parietal periventricular regions were performed with a software program (Functool). While measuring ADCav values, the Region of Interest (ROI) was drawn simultaneously on both conventional MR images and ADC map to confirm exact localization. The values noted in each ROI were surface area, mean, SD, minimum and maximum values.

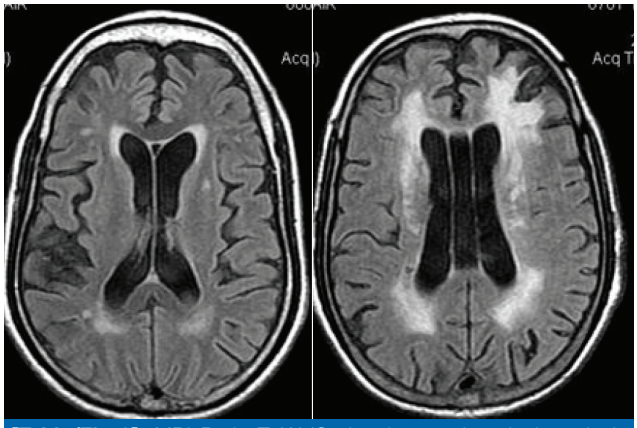


[Table/Fig-1]: MRI brain T2W IS showing grade 1 leukoaraiosis - hyperintense, tiny [<5mm] and discrete periventricular white matter lesions. **[Table/Fig-2]:** MRI Brain T2W IS showing grade 2 leukoaraiosis - hyperintense, small (5-10 mm) and discrete periventricular white matter lesions.

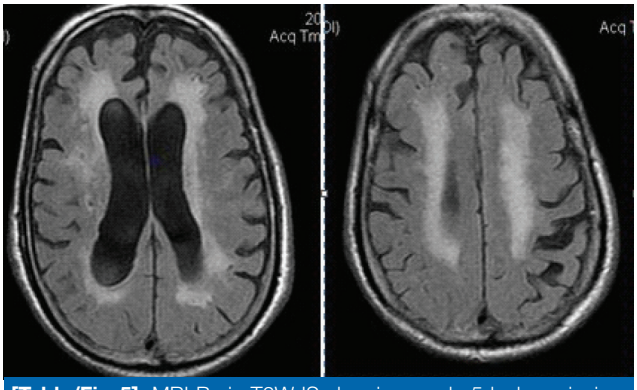
Leukoaraiosis Grading

Grading of leukoaraiosis was done based on modification of Fazekas Scaling System [11,12]. In Fazekas scale, there is different grading followed for deep white matter and periventricular white matter lesion based on the size and shape of the lesions. In our study we grouped all the lesions under one scaling system and grouped them into five grades according to their size, shape and confluence:

Grade 1– discrete, small <5mm (n=8) [Table/Fig-1]; Grade 2- discrete lesions, 6-10mm (n=16) [Table/Fig-2]; Grade 3- discrete but confluent lesions, 11-25 mm (n=13) [Table/Fig-3]; Grade 4- diffusely confluent lesions, >25 mm (n=21) [Table/Fig-4]; and Grade 5 - diffuse lesions involving major part of WM (n=2) [Table/Fig-5].



[Table/Fig-3]: MRI Brain T2W IS showing grade 3 leukoaraiosis - hyperintense, patchy and non confluent periventricular white matter lesions. **[Table/Fig-4]:** MRI Brain T2W IS showing grade 4 leukoaraiosis - hyperintense, patchy and confluent periventricular white matter lesions.



[Table/Fig-5]: MRI Brain T2W IS showing grade 5 leukoaraiosis – extensive hyperintense, patchy and confluent lesions involving most of the periventricular white matter.

Assessment of Cognition

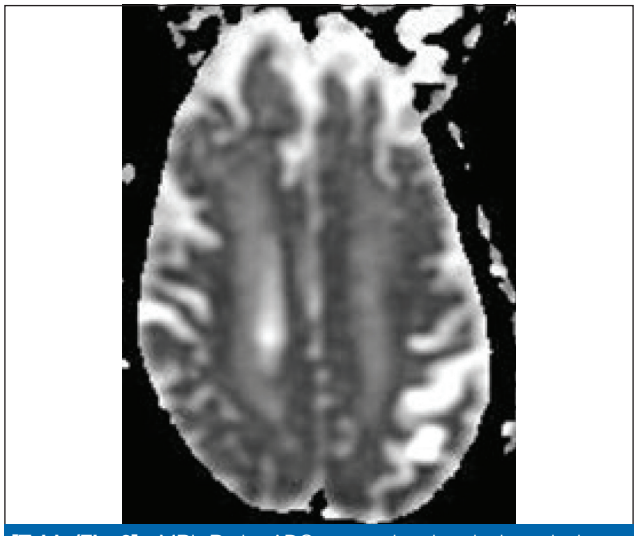
To evaluate the cognitive function of the leukoaraiosis patients, we employed Mini Mental Status Examination (MMSE). MMSE is a questionnaire with 11 questions which assess all the components of cognition, namely the attention and calculation, registration, recall, ability to follow simple commands and orientation and language. MMSE maximum score is 30. Score of 23 or less in literate and score less than 19 in illiterate subjects indicates impairment of cognition [13,14].

STATISTICAL ANALYSIS

The proportion was reported with its 95% Confidence Intervals (95% CI) wherever it was required and χ^2 statistics was applied to test the association between two categorical variables. Two sample t-test was applied to test the difference between the mean of two different groups (case v/s control), if data was normally distributed. Otherwise Mann-Whitney test was applied. One way analysis of variance (One-way ANOVA) was used to test the differences in means among >2 groups (LA grade) in case of normally distributed data otherwise Kruskall-Wallis test was applied. The variables which were found significantly associated with LA grade at $p<0.05$ were considered for modeling. Ordinal logistic regression was done to adjust for the confounding variables and adjusted odds ratios with their 95% CI and exact p-value were reported for LA grade. Data were analysed using statistical software package, STATA 9.2 and the difference was considered to be significant if 'p' value was found to be <0.05.

RESULTS

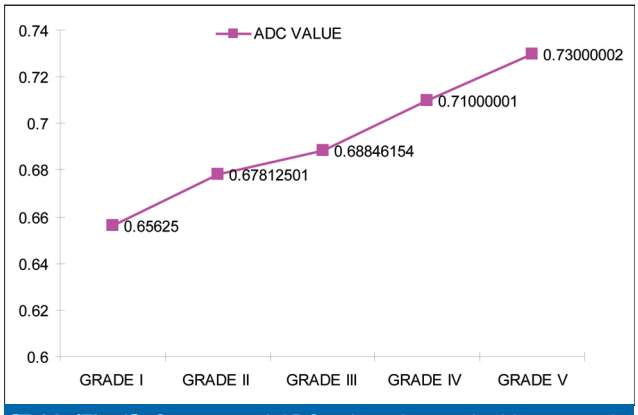
The result of this study has been given in the form of following tables and graphs. Leukoaraiosis lesions were identified to be non restricting lesions on DWIs and hyper intense on the ADCav maps [Table/Fig-6], We observed the ADCav values of the leukoaraiotic regions being higher than that of normal white matter and the values proportionately increased with the grade of the lesions [Table/Fig-7], with significant p-value of <0.001. There was minimally significant difference found between the ADCav values of the normal WM of the patients with leukoaraiosis (group 1 as a whole) (mean = 0.69 , min = 0.64, max = 0.74) and those of the control group (mean 0.64, min = 0.63, max = 0.67) (group 2). However, after detailed analysis within group 1, we found the ADCav values of normal white matter were higher as the grade of leukoaraiosis was higher (p-value <0.001 for all) [Table/Fig-8]. We were able to evaluate MMSE in 51 out of 60 patients only. Significant association found between reduced MMSE and presence of leukoaraiosis (p-value< 0.001). Proportional reduction of MMSE score with increasing grade of Leukoaraiosis (p-value <0.001) was also observed [Table/Fig-9].



[Table/Fig-6]: MRI Brain ADC map showing leukoaraiosis as hyperintense lesions.

Grade of Leukoaraiosis	ADCav Value of Leukoaraiosis	
	Min. Value	Max. Value
Grade I	1	1.14
Grade II	1.15	1.21
Grade III	1.21	1.24
Grade IV	1.25	1.35
Grade V	1.30	1.31

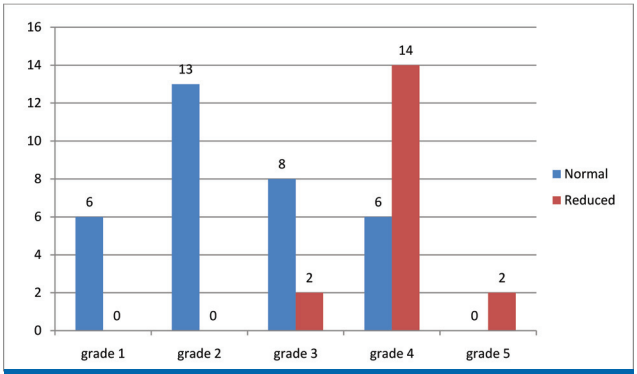
[Table/Fig-7]: Summary of ADCav values in regions of leukoaraiosis in different grades.
The ADC value increased proportionally with grade of Leukoaraiosis
p-value ≤ 0.0001



[Table/Fig-8]: Summary of ADC value of normal white matter in leukoaraiosis patients with grading.

DISCUSSION

Leukoaraiosis, synonym of ischaemic demyelination, is described as bilateral discrete focal or diffuse patchy CT hypodense and MR T2W hyperintense cerebral white matter lesions. These lesions are presumed to be resulting from deep penetrating vessels arteriosclerotic changes supplying the periventricular white matter which is deprived of collateral blood supply



[Table/Fig-9]: Correlation of MMSE with leukoaraiosis grade (n=51).

[2,12]. Pathologically loss of axons and glial cell proliferation marks the leukoaraiosis [1]. The term "leukoaraiosis" arrived from the Greek ("leuko" = white and "araios" = rarefaction) and was initially suggested by Vladimir Hachinski, who was an Ukrainian-born Canadian neurologist [15].

Leukoaraiosis, were identified to be non restricting lesions on DWIs and hyperintense on the ADCav maps in our study. This finding could be explained by the axonal loss in these lesions which generally cause major restriction to diffusion of water. Adding to this effect the increased water content secondary to axonal loss could also contribute to this hyperintense signal on ADC images[1,16].

The proportionate increase in the ADCav values with rising grade of the leukoaraiotic lesions could represent the extent of axonal loss in the lesions. This could also be used as an alternative grading scale to assess the severity of the leukoaraiosis. Few studies have shown that the ADCav values of leukoaraiosis lesions are useful in differentiating the sub-acute and chronic ischaemic stroke lesions at few a times when it is difficult only with conventional MR imaging [11,17,18].

The higher ADCav values of normal white matter in patients with high grade leukoaraiosis lesions in comparison with normal white matter in healthy subjects could represent the possibility of early leukoaraiosis pathology in those white matter areas appearing normal on conventional MR imaging. The chances of averaging effect from leukoaraiosis lesions in the normal white matter areas while ADCav measurement could be excluded, as we carefully selected the ROI on both T2WIs and DWI. Hence, apart from giving the information regarding severity of leukoaraiosis, DWI and ADC values measurement could also help us to find the normal appearing white matter on conventional MRI, which could tentatively develop leukoaraiosis lesions over time and hence in estimation of exact and complete extent of the disease.

Helenius J et al., studied leukoaraiosis on 1.5T conventional MR images, DWI and ADC. They have included 85 leukoaraiosis patients and compared them with 22 healthy controls without leukoaraiosis lesions. In estimation of ADCav values in leukoaraiosis regions and normal white matter they found higher ADC value with increasing grade of the lesions (0.92 to 1.27) which was essentially greater than the values in normal white matter (0.69 ± 0.04). They concluded that the leukoaraiosis lesions display significant change in the ADCav values when compared with normal white matter [12]. In our study the ADC values of the leukoaraiosis lesions were ranging from 1-1.31 and the values in the normal white matter in patients with leukoaraiosis were ranging from 0.65 - 0.73, which is close to the value in the study described above. Comparison of our study and this study has been tabulated

Parameters	Present study	Study by Helenius J et al., [12]
No. of Cases – (Leukoaraiosis Patients)	60	85
No. of Controls – (Healthy Subjects)	20	22
Mean ADC in Leukoaraiosis Lesions	1-1.31	0.92 to 1.27
Mean ADC in Normal White Matter	0.65 - 0.73	0.69 ± 0.04
Association between reduced MMSE and presence of Leukoaraiosis	Assessed and significant association found	Not assessed
Difference of ADC values of Leukoaraiosis Lesions and Ischemic Stroke of Different Stages	Not assessed	Assessed and found significantly different ADCav values in leukoaraiosis lesions and infarcts of different stages like 6 hours, 24 hours ,1 week, one-month and 3-month-old infarcts

[Table/Fig-10]: Comparison of our study with a previous similar study.

[Table/Fig-10].

Mario M et al., tested whether analysis of the whole brain ADC histogram (WB-ADC) could be used as an alternative method to visual scoring of leukoaraiosis on T2WIS. They generated ADC maps and acquired ADC histograms from it. They found the ADC histogram median value of whole brain was directly correlating with visual leukoaraiosis severity grading (p-0.013). They concluded that the WB-ADC histogram is a reliable alternative method to assess the extent and severity of the leukoaraiosis [19].

Calli C et al., assessed the appearance of periventricular ischemic lesions on MRI and estimated the ADC values in the regions of leukoaraiosis. Total 78 patients with leukoaraiosis lesions, few of them having acute and chronic infartcs in

white matter were imaged with conventional sequences of MRI and DWI. ADC values of the white matter infarcts and leukoaraiosis regions were measured and was observed to be characteristically varying from each other with p-value of <0.05. They concluded as DWI is mandatory in distinguishing leukoaraiosis from white matter infarcts in periventricular location in acute stage [20].

In this study the observation of significant association of reduced MMSE score with leukoaraiosis (p-value<0.001) and proportional reduction of MMSE score with increasing grade of leukoaraiosis (p-value<0.001) could suggest leukoaraiosis as one of the causative factor of impaired cognition and could help us to assess the prognosis of these patients, presumed to be poor in patients with severe grade of leukoaraiosis.

Briley DP et al., has done a study in which they followed 221 patients prospectively and evaluated them for severity of leukoaraiosis and given a conclusion that severity of leukoaraiosis predicts morbidity and mortality independently of preexisting neurological deficit [21].

A study was done in a large set of people in 2003, by Geroldi C et al., with an objective to find the correlation of minimal or mild nonamnestic cognitive impairment with vascular risk factors and association of cognitive impairment with Parkinsonism and gait disturbance. They found three most commonly associated vascular risk factors of cognition impairment being hypertension, atrial fibrillation or other ECG changes and reduced levels of HDL cholesterol. Cognitive dysfunction with subcortical features was significantly associated with cerebro-vascular risk factors (p=0.001) [22].

Lovblad K, et al., studied the patients with mildly impaired cognition on MRI and observed the ADC Map frontal lobes. Deep white matter ischaemic changes were found in 37.5% of patients with mild cognitive dysfunction. It is typical for this category of patients the presence of leukoaraiosis on MRI. The study revealed that, leukoaraiosis lesion presence and extent are poor prognostic factors to develop dementia later, especially when it is associated with corpus callosal and generalized brain atrophy [23].

The relationship of white matter lesions with mood and cognition was studied by Pantoni. They evaluated the clinical relevance of age related white matter changes (ARWMC), especially with vascular cause of depression in elderly. They found, ARWMC to be significantly associated with mild cognitive impairment and increased risk of developing dementia. Apart from impaired cognition, severe depressive symptoms were observed in patients having significant ARWMC, when compared with patients not having the ARWMC or having mild ARWMC [24].

In total it is suggested that both the cognition dysfunction and leukoaraiosis are significantly associated with vascular risk factors and they are associated with each of them too. Our study results saying that leukoaraiosis could forecast the impairment of cognition in early stage are supported by these studies.

An attempt to grade the leukoaraiosis lesions based on the mean ADC values employed in our study is new in the research field and the literature.

LIMITATIONS

In the present study, precise age and sex matching between group 1 patients with leukoaraiosis and group 2 healthy subjects was not possible. It could be the limitation of our study, however all the subjects in group 1 and 2 were above 50 years of age which is the common age group and one of the significant risk factor to develop leukoaraiosis.

CONCLUSION

We have drawn the following conclusions from our study. The ADC values of leukoaraiosis lesions proportionately increase with the grade of the lesions and could be used as a grading scale of Leukoaraiosis. ADCav values of normal white matter in patients with leukoaraiosis are higher when compared with healthy subjects with no leukoaraiosis and were found to rise with increasing grades of leukoaraiosis, this could help us to find the white matter that appears normal on conventional MRI, which is prone to develop leukoaraiosis over time and to assess the complete extent of the lesion. Significant association of leukoaraiosis was observed with impaired cognition, proposing leukoaraiosis as one of the cause for cognitive function.

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