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Original Article

Radiology Section

Ischemic Demyelination and Ischemic Stroke on Diffusion Weighted MR Imaging and Risk Factors of Ischemic Demyelination

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ABSTRACT

Introduction: Bilateral periventricular and subcortical white matter lesions of brain, which could be small, discrete or patchy confluent appearing hypodense on Computed Tomography (CT) and hyperintense on T2 weighted MRI are called Ischemic Demyelination (ID). This radiological finding is common in elderly people and presumed to arise secondary to small vessel ischemia. However, the risk factors, underlying pathogenesis and clinical importance of this condition is still under investigations.

Aim: To evaluate use of apparent diffusion co-efficient values in distinguishing ID from ischemic infarct, to find the correlation between ID and ischemic stroke and to list out the risk factors of ischemic demyelination.

Materials and Methods: We studied 60 patients with ID. Out of them 44 patients with ischemic strokes were further divided into 6 small groups based on duration of stroke. All subjects were studied on conventional MRI and Diffusion Weighted Imaging (DWI). ADCav values were determined for the regions of ID and infarcts. Detailed clinical history of all the subjects was obtained. Total serum cholesterol done for all.

Results: Mean ADC value of ischemic infarcts with duration up to one month, 1-3 month and >3 months were lesser, overlapping and higher than the values of ID lesion respectively with p-value <0.05. Significant association of ID and ischemic stroke, especially of lacunar type infarct was found. Significant association of ID found with elderly age, history of hypertension, diabetes mellitus. Smoking, alcoholism, gender, history of ischemic heart disease, peripheral vascular disease and high total serum cholesterol levels did not show significant association with ID.

Conclusion: ADCav value estimation can be applied in overcoming pseudo-normalization of subacute infarcts around one week and to distinguish >3 months old chronic infarcts from ID lesions. The significant association of ID with lacunar infarct favors the chances of common pathogenesis, the small vessel ischemia. With this evidence ischemic demyelination can be proposed as a risk factor to stroke attack. Increasing age, history of hypertension, diabetes mellitus are found to be the risk factors for development of ID.

Keywords: ADC pseudo-normalization, Lacunar infarct, Leukoaraiosis

INTRODUCTION

Bilateral periventricular and subcortical white matter lesions of brain, which could be small, discrete or patchy confluent appearing hypodense on CT and hyperintense on T2 and T2 FLAIR MRI (T2W, T2 FLAIR MRI) are called ischemic demyelination (ID). It has the synonym of leukoaraiosis [1]. These radiological findings are presumed to arise secondary to small vessel ischemia.

This radiological finding is commonly seen in elderly people (>65 years). Aging, hypertension, diabetes mellitus and ischemic heart disease are considered to be risk factors resulting in development of ID. Though most are asymptomatic, some of the individuals with this finding present with significant clinical features like depleted cognition, disturbed gait and dementia [2-4]. However, the risk factors, underlying pathogenesis and clinical importance of this condition is still under investigations. Few studies have shown ID as one of the risk factors for developing ischemic stroke and overall accentuation of morbidity and mortality of the patient is noted to correlate significantly with increasing grades of ID [5-7].

MATERIALS AND METHODS

This single blinded prospective study was done at M.R.I. unit of Department of Radio diagnosis, C.S.M. Medical University, Lucknow, India, during the period of one year in 2009. Ethical committee clearance was acquired for the study. Consent was acquired from all the subjects who were included in the study. All the patients, above 50 years of age who were referred for MRI brain and showed ID lesions were included in the study. The patients with multiple white matter lesions other than ID and patients with hydrocephalus and trans-ependymal CSF leak were excluded from this study.

The study was done in a group of 60 subjects with ID of different grades (with age above 50 years, 35 men, 25 women) including patients with ischemic stroke (n=44). Patients with both ischemic demyelination and ischemic stroke were again divided into 6 groups based on the stage of the infarct. Group-1: Less than 6 hours (n=4); Group-2: 6 hours to 24 hours (n=4); Group-3: 24 hours to 1 week (n=6); Group-4: 1 week to 1 month (n=8); Group-5: 1 month to 3 months (n=12) and; Group-6: More than 3 months (n=10). Ischemic stroke patients were also subdivided based on the type of the infarct, like lacunar infarct or cortical infarcts.

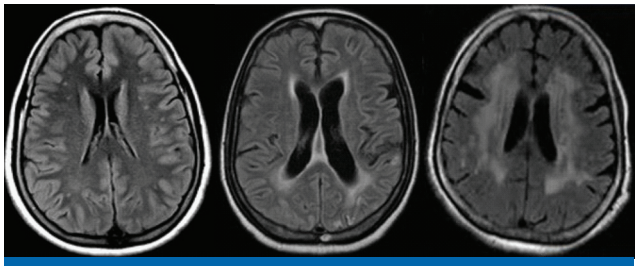
With the use of the questionnaire, detailed clinical history of all the patients was obtained including patient's age, sex, history of smoking, alcoholism, hypertension, diabetes mellitus, ischemic heart disease, peripheral vascular disease. All the patients total serum cholesterol level was estimated and noted. Patient's clinical history and lab reports were blinded for the radiologist reporting the MRI.

Imaging Technique

All the 60 subjects were imaged with conventional T1WIs, T2WIs and T2 FLAIR sequences on 1.5 T GE (Signa) MR machine. DWI sequence was done with echo-planar imaging (EPI) with two b values, 0 and 1000 s/mm^2 with following parameters: TR 4024 ms, TE 120ms, 20 slices of 5 mm thickness, interslice gap of 1 mm, field of view 230×230 mm^2, and matrix size 152×10^5 interpolated to 256×256. From diffusion images ADCav maps were acquired. Estimation of ADCav values (10^{-3} mm^2/s) in regions of ID and ischemic stroke in different stages were done by a software program (Functool). In each region of interest, minimum, maximum values and mean were calculated.

Grading of Ischemic Demyelination

ID was graded based on modification of the established grading scale, Fazekas Grading Scale [8,9]. Based on the size and shape the lesions ID is divided into 5 groups. Grade-1: small, focal <5mm lesions (n=8) [Table/Fig-1a]; Grade-2: large focal, 6 to 10 mm lesions (n=16); Grade-3: patchy, focal confluent, 11 to 25 mm lesions (n=13) [Table/Fig-1b]; Grade-4: diffusely confluent, >25 mm lesions (n=21); and Grade-5: lesions affecting the most of the WM (n=2) [Table/Fig-1c].



[Table/Fig-1a,b&c]: (a) Axial T2 FLAIR image showing multiple tiny (<5mm) hyperintense white matter lesions; (b) Axial T2 FLAIR image showing small patchy hyperintense periventricular white matter lesions; (c) Axial T2 FLAIR image showing extensive diffuse confluent hyperintense white matter lesions.

STATISTICAL ANALYSIS

The χ^2 statistics was used to estimate the test the two categorical variables association and the proportion was measured with its 95% confidence intervals (95% CI) wherever it was needed. To measure the difference of mean between two groups, two sample 't'-tests were used if data was normally distributed or else Mann-Whitney test was used. To measure the difference of mean among more than 2 groups (grading of ID), One-way-ANOVA was applied if the data was distributed normally, or else Kruskall-Wallis test was used. Association of different variable with ID was considered significant if value of p was <0.05. Confounding variables are adjusted with ordinal logistic regression and odds ratios adjustment and exact p-value were reported with their 95%CI for ID . STATA 9.2, a statistical software package was applied to analyze the data.

RESULTS

The ADC values (10^{-3} mm^2/s) of ID were noted to increase proportionally with grades of the lesion (p-value – 0.0001). In Grade 1 to Grade 5 mean value was ranging from 1.1 to 1.3 with minimum value of 1.015 and maximum value of 1.350 [Table/Fig-2], Ischemic infarcts up to one month duration showed mean ADC value that is lesser than ID (p-value≤0.001). One to three month old infarct showed mean ADC values

Grade of Ischemic Demyelination	ADC Value of Ischemic Demyelination	
	Min. Value	Max. Value
Grade I	1.015	1.136
Grade II	1.152	1.214
Grade III	1.223	1.244
Grade IV	1.256	1.350
Grade V	1.300	1.350

[Table/Fig-2]: List of minimum and maximum ADCav values of ischemic demyelination in different grades.

which overlap with that of ID (p-value–0.015). More than three month old infarcts showed mean ADC values that are greater than that of ID (p-value-0.01) [Table/Fig-3], For the association of ID and ischemic stroke, p-value of significance was 0.003 and for the association of ID and lacunar infarct p-value was 0.574. Proportion in 95% confidence limit was - 71, 91 [Table/Fig-4].

	Upto 1 Month	1-3 Month	More than 3 Month
Infarct	0.44	1.17	1.50
Leukoaraiosis	1.18	1.21	1.27

[Table/Fig-3]: Comparison of ADCav values (10^{-3} mm^2/s) of ischemic stroke in different stage with leukoaraiosis.

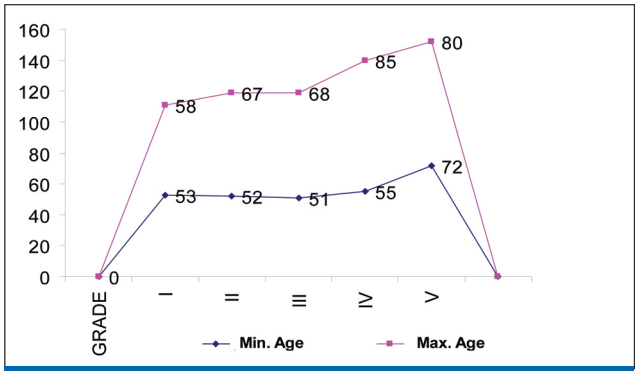
Infarct	Grade I	Grade II	Grade III	Grade IV	Grade V
Lacunar Infarct	7	13	10	19	1
Cortical Infarct	1	3	3	2	1

[Table/Fig-4]: Enumeration of number of patients with ischemic demyelination in different grades showing cortical and lacunar ischemic stroke.

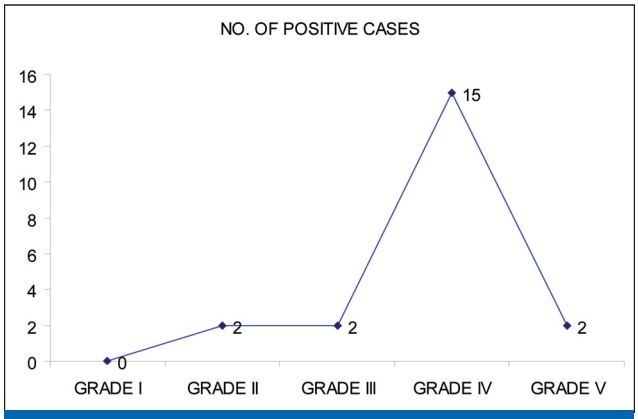
In our study group patients were between the age group of 50-81 years. Elder the patient was, higher was the grade of the ID found (p-value≤0.001). The mean age based on grade of the ID lesions was as following:

Grade-1 (mean age 54.75); Grade-2 (mean age 58.5); Grade-3 (mean age 60.5); Grade-4 (mean age 65.3) and; Grade-5 (mean age 76) [Table/Fig-5].

Significant association was found between hypertension and ID with 50% of the patients with ID (Group 1) having history of hypertension showing a probability value of 0.021 [Table/Fig-6]. History of diabetes mellitus (p-value=0.003), has also shown significant association with development of ID. Previous history of ischemic heart disease (p-value = 0.131), peripheral vascular disease (p-value=0.664) and high total serum cholesterol levels (p-value=0.100) have not shown any significant association with development of ID. History



[Table/Fig-5]: Enumeration of significant association of elderly age with ischemic demyelination.



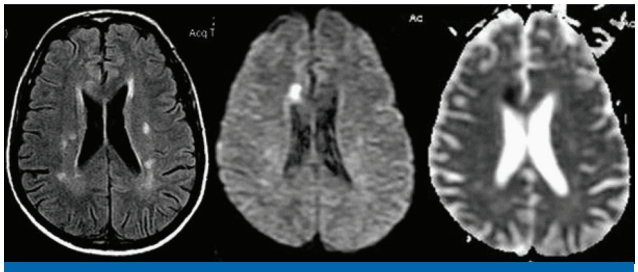
[Table/Fig-6]: Demonstration of significant association of hypertension and ischemic demyelination.

of smoking (p-value=0.495), alcohol intake (p-value=0.627) and sex distribution (p-value=0.995) also does not showed any significant association with development of ischemic demyelination.

DISCUSSION

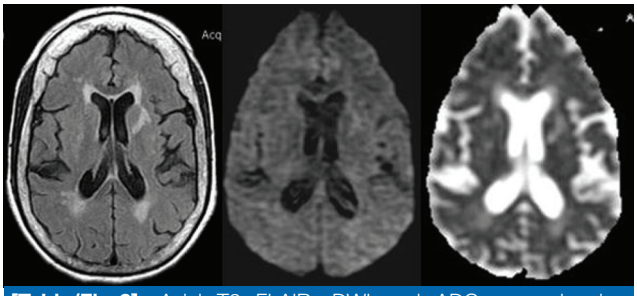
Bilateral white matter lesions of brain, which could be small, discrete or patchy confluent appearing hypodense on CT and hyperintense on T2 and T2 FLAIR MRI (T2W, T2 FLAIR MRI) are called ID with the synonym of leukoaraiosis [1]. On DWI these lesions were not showing restriction and appeared hyperintense on ADC, with ADC values higher than that of the normal white matter. ADCav values were observed to be steadily increasing with the grade of the lesions. This finding is presumed to be secondary to axonal loss and proliferation of glial cells found in the regions of ID on pathology specimens. As axons cause hindrance to water diffusion, loss of axons is considered to accentuate the water diffusion [9].

There is decreased ADC values in the hyper-acute and acute infarcts [Table/Fig-7], which could be secondary to significant loss of water in the cells making the lesions to appear hypointense on ADC map. This makes it clear that on DWI and ADC maps we could easily differentiate the infarcts from the ischemic demyelination visually itself and there is no



[Table/Fig-7]: Axial T2 FLAIR, DWI and ADC map showing acute infarct in right frontal white matter appearing hyperintense on FLAIR, bright on DWI and hypointense on ADC map. Grade I ID lesions in the bi-parietal region appearing hyperintense on both T2 FLAIR and ADC map with no diffusion restriction.

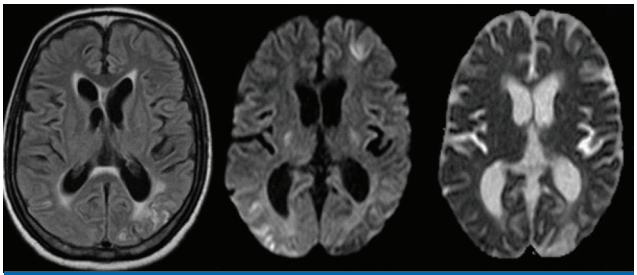
need for ADC value estimation. Ischemic infarcts that are one week old generally show pseudo-normalization on ADC map, appearing hyperintense, making it difficult to differentiate it from the ID lesions [Table/Fig-8]. Though, these infarcts in sub-acute stage appear visually same as ID lesions on DWI and ADC map, ADCav values were significantly different in both type of lesions, being lesser in infarct than the ID which could help us to differentiate the lesions from each other.



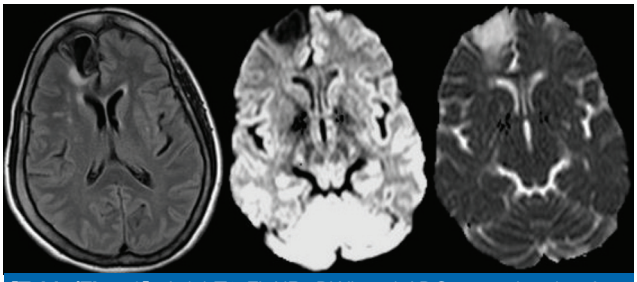
[Table/Fig-8]: Axial T2 FLAIR, DWI and ADC map showing subacute infarct on 8th day in left internal capsule anterior limb, appearing hyperintense on both T2 FLAIR and ADC map with no restriction on DWI representing pseudo-normalization. Grade-2-3 ID lesions in the bi-frontal and parietal periventricular white matter also appearing hyperintense on both T2 FLAIR and ADC map with no diffusion restriction.

As the ADC values of infarcts that are 1-3 month old are overlapping with that of the ID lesion [Table/Fig-9], measuring ADCav values is not much useful at this stage. Significantly higher ADCav values in chronic infarcts (>3-month-old) than that of ID lesions [Table/Fig-10], could be explained by the increased water content in the chronic infarcts regions in comparison with the ID lesions. Though, on ADC mapping these two lesions appear similar with the use of ADCav values these can be differentiated [10,11].

In our study the proportion of patients with ID and ischemic infarcts were found to be significant (95% confidence limit – 60, 83). Out of the lacunar and cortical infarcts the proportion of patients found (95% confidence limit 71, 91) with lacunar infarct and ID was more significant than that of cortical infarct.



[Table/Fig-9]: Axial T2 FLAIR, DWI and ADC map showing one month old subacute infarct in left posterior parietal cortex, appearing hyperintense on both T2 FLAIR and ADC map with no restriction on DWI. Grade-3 ID lesions in the bi- frontal and parietal periventricular white matter also appearing hyperintense on both T2 FLAIR and ADC map with no diffusion restriction.



[Table/Fig-10]: Axial T2 FLAIR, DWI and ADC map showing four month old chronic infarct in right basi-frontal lobe, isointense to CSF T2 FLAIR and hyperintense on ADC map with no restriction on DWI. Multiple discrete tiny Grade 1 ID lesions in the right frontal white matter appearing hyperintense on both T2 FLAIR and ADC map with no diffusion restriction.

Though the association of ID with ischemic strokes was showing significant p-value (0.003), the p-value for association of lacunar infarct type with ID was not significant (0.574). This could be either due to the lack of normal distribution of variables secondary to small number of cases included or due to real lack of association between these variables.

Though, few related studies have shown significant association of ID with cerebro-vascular attack, especially lacunar infarct [12], one study done in large number of stroke patients in Danish stoke section did not showed any significant association between ID and ischemic infarcts [13]. This could also be attributed to this study design, where ischemic infarcts were not divided into different types like cortical and lacunar infarcts, allowing cortical infarct to act like a negative modifier of the association.

ID was proposed to be an independent risk factor for development of ischemic stroke, especially lacunar type by another study [14] which is likely caused by the same underlying small-vessel pathology. Though, it is found that ID predisposes to lacunar type of infarct, it is also found to be a risk factor for development of cortical stroke and intra-cerebral hemorrhage. In a study which evaluated the relationship of ID with ischemic infarct has shown ID, apart from being an independent risk factor it also predicts the morbidity and mortality of the patients [6]. Hence, every physician should be informed about the significant association of ID with stoke and preventive treatment for stroke should include proper management of ID risk factors too.

The significant association found between increasing age (>50 years), long standing history of hypertension, diabetes mellitus, history of ischemic strokes with the presence of ID could propose these factors to be risk factors for the development of ID. Association of all these variables was found to be more with higher grades of (Grade-4 and 5) ID. There are few other studies which have also proved age as the most important risk factor for development of ID [14-16]. Few studies have found impaired glucose tolerance, dyslipidemia including

increased triglycerides and reduced HDL levels showing significant association with ID and as well as cerebro-vascular attack [16,17].

The small number of patients having history of smoking and alcohol intake being included in our study could be the limitation of our study, which could be one of the possible reason for the result showing no significant association of these histories with the presence of ID, however none of the related studies has shown significant relationship of either these variables with development of ID. The absence of significant association between ID and high total serum cholesterol level, ischemic heart disease and peripheral vascular disease history could be due to the small number of the sample or else due to the absence of the association in real. One other limitations of our study is the small number of patients with ID and ischemic stroke in Group 1 to 3. Significant numbers of studies are required to substantiate our hypothesis.

Most of the studies about pathogenesis of ID have suggested various causes, most common of them being the theory of chronic hypo perfusion. Deep white matter ischemia, dysregulation of blood pressure and CSF flow disturbance [18-22] are proposed to be the underlying pathology for the development of ischemic demyelination.

Aging which is found to be the most common risk factor for ID development [17] and all the other additional risk factors like hypertension, diabetes mellitus, and ischemic heart diseases are found to be common in precipitating an abnormality in cerebral vascular channels, especially the small penetrating arteries supplying the white matter. That is nothing but arteriosclerosis, which is basically replacement of vascular channel wall smooth muscle with hyaline and fibrous material resulting in wall thickening and luminal narrowing [22]. Pathological specimens from areas of ID consistently showed the presence of arteriosclerosis in the penetrating arteries. This abnormality could result in local ischemia causing axonal loss identified as ID or necrosis seen as lacunar infarcts on imaging depending upon the severity of ischemia.

CONCLUSION

The regions of ID shows significantly higher ADCav values than the normal white matter. Though, DWI and ADC mapping are not much distinguishing between ischemic demyelination and pseudo-normalization of subacute infarcts (around one week age) and the chronic infarcts (>3 months), ADCav value estimation can be used to differentiate those lesions from ID . The observation of significant association of ID and ischemic stroke, predominantly the lacunar type favors the chance of similar pathogenesis in both these conditions. With this evidence ID can be proposed as one of the risk factor to the development of stroke. This signifies the essence of inclusion of ID risk factor control as a part of stroke prevention activity.

Increasing age, history of hypertension, diabetes mellitus and cerebro-vascular disease are found to be risk factors for development of ID. Especially when the numbers of risk factors are higher there are more chances for the patient to develop higher grades of ID.

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