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ASSOCIATION OF LEUKOARAIOSIS WITH CLINICAL OUTCOME IN ISCHEMIC STROKE: A CROSS-SECTIONAL ANALYTICAL STUDY

Neurology

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ABSTRACT

Background And Purpose: Cerebral Leukoaraiosis or white matter hyperintensities are frequently seen in acute stroke, but its clinical consequences on functional recovery are less studied. We aimed to determine the various risk factors associated with leukoaraiosis and to correlate leukoaraiosis with poor clinical outcomes post-stroke. **Methods:** 100 patients with acute stroke were included in the study and were evaluated at presentation and 3 months post-stroke with NIHSS and MRS scores. All patients underwent an MRI and leukoaraiosis was graded using the Fazekas scale. **Results:** 64 % of the study population had leukoaraiosis. Severe leukoaraiosis was seen in 19%, moderate in 22%, mild in 23% and 36% had no leukoaraiosis. White matter hyperintensities are common in hypertensives and those above 65 years of age. In multivariable analysis age, initial NIHSS score, and severe leukoaraiosis were independent predictors of poor outcome at 3 months post-stroke. **Conclusion:** Severe WMH were independently associated with poor functional outcome in post-stroke patients

KEYWORDS

leukoaraiosis ,WMH (white matter hyperintensities)

INTRODUCTION

Leukoaraiosis or white matter hyperintensities (WMH) are cerebral white matter changes frequently observed on CT or MRI in the brains of elderly subjects, particularly in those with vascular risk factors [1]. It has been proposed to represent an imaging marker of brain frailty and biological age. Advanced age and hypertension have been consistently reported to be highly associated with LEUKOARAIOSIS [2].

Although leukoaraiosis has long been considered an incidental finding with no therapeutic necessity, there is now growing evidence linking it to, cognitive impairment and a high risk of death after stroke. (3) Its pathogenesis is still unclear, common mechanisms proposed are cerebral blood flow dysregulation, venous collagen deposition, blood-brain barrier (BBB) disruption, invalid neurovascular coupling, and genetic factors .(4,5)

AIMS AND OBJECTIVES

In this study, we aimed to determine various risk factors associated with Leukoaraiosis and whether pre-existing leukoaraiosis, independently predicts the degree of functional recovery post-stroke as assessed by the modified Rankin scale (MRS)

METHODS

This study was reviewed and approved by our Institutional Review Board. We analyzed 100 stroke patients admitted to our centre over a period of 18 months. Patient demographics, co-morbidities, medication, type of stroke as per TOAST classification and thrombolytic treatment were noted in all patients. NIHSS and MRS scores were assessed at the time of presentation and reassessed at 90 days post-event. All included patients (n = 100) underwent brain MRI. Leukoaraiosis was graded on FLAIR MRI by Fazekas scale based on visual assessment of both periventricular (0 = absent, 1 =caps or pencil lining, 2 = smooth halo, 3 = irregular periventricular hyperintensities extending into deep white matter) and subcortical areas (0 = absent, 1 = punctuate foci, 2 = beginning confluence of foci, 3 = large confluent areas). Based on this grading we divided leukoaraiosis into mild, moderate, and severe Perivascular spaces, and lacunes of presumed vascular origin were excluded.

Statistics

Data were presented as mean, standard deviation, frequency, and percentage. Categorical variables were compared using the Pearson chi-square test. Significance was defined by P values less than 0.05 using a two-tailed test. Covariates with P less than 0.05 in bivariate analyses were entered into the multivariable analysis. we performed multiple ordinal logistic regression analysis with modified Rankin Scale scores as an ordinal outcome variable to identify the independent predictors. Data analysis was performed using IBM-SPSS version 21.0

RESULTS

The median age in our study population was 59 years. 66% were men and 32.3% were women. Table .1 summarizes the study population's demographic, clinical and imaging characteristics.

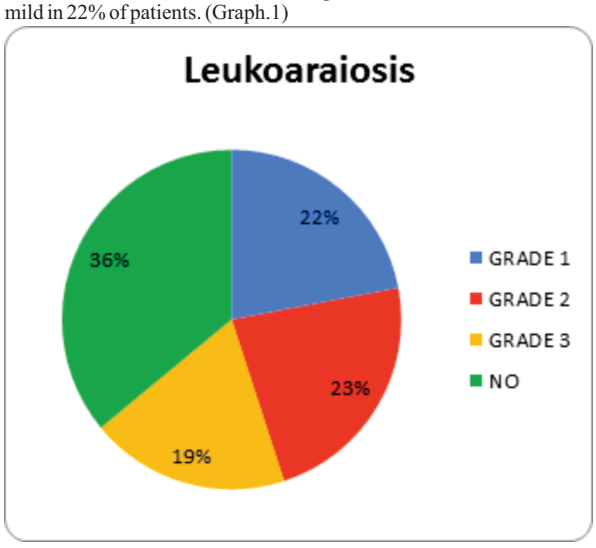
Table.1 Demographic, Clinical And Imaging Characteristics Of The Study Population

AGE GROUP	<30	5
	31-40	5
	41-50	15
	51-60	14
	61-70	39
	>71	22
SEX	MALE	66
	FEMALE	34
HYPERTENSION	NO	50
	YES	50
CHOLESTEROL	NO	80
	YES	20
DYSLIPIDEMIA	NO	77
	YES	23
DIABETES	NO	56
	YES	44
SMOKING	NO	75
	YES	25
ALCOHOL	NO	69
	YES	31
NIHSS SCORE AT ADMISSION	<4	40
	5-15	49
	16-20	10
	>21	1
MRS SCORE AT 3 MONTHS	<3	89
	>3	11
LEUKOARAIOSIS	GRADE 1	22
	GRADE 2	23
	GRADE 3	19
	NO	36
TYPE OF STROKE	CARDIOEMBOLIC	14
	LAO	46
	OTHER ETIOLOGY	3
	SVO	36
	UNDETERMINED	1

THROMBOLYSIS	NO	83
	YES	17

Among the enrolled patients, 50% had hypertension, 44 % were diabetic, and 23% had dyslipidemia. 31% and 25% of the subjects were alcoholics and smokers respectively. The mean NIHSS score at presentation in our patients was 7. Large artery stroke was seen in 46%, small vessel stroke in 36%, 14% had cardioembolic and 3% had a cryptogenic stroke. 17% of our patients underwent thrombolysis.

64% of patients had WMH and 36 % of patients did not have WMH. Leukoaraiosis was severe in 19% of patients, moderate in 23%, and mild in 22% of patients. (Graph.1)



Graph.1. Prevalence Of Leukoaraiosis

When comparing patients with no or mild WMH, those with severe WMH were older, smokers and more frequently had a history of hypertension. In univariable analysis, old age, hypertension, and smoking were found to be associated with severe WMH. In multivariable logistic regression analysis, old age, and hypertension were independently associated with severe WMH (Table 2).

Table2:Multivariable Analysis of Risk factors associated with Leukoaraiosis

	Leukoaraiosis				
	GRADE 1	GRADE 2	GRADE 3	NO	P value
HYPERTENSION	15	12	12	11	0.021
CHOLESTEROL	3	7	3	7	0.505
DYSLIPIDEMIA	4	7	3	9	0.649
DIABETES	6	15	6	17	0.045
SMOKING	7	5	5	8	0.839
ALCOHOL	6	6	6	13	0.839
AGE GROUP	<65 12	14	9	32	0.005
	>66 10	9	10	4	

In our study, Poor functional outcomes as estimated by MRS at 3 months were more common in those with severe WMH. In multivariable analysis, initial NIHSS, Age, and severe WMH were independent predictors of poor functional outcome post-stroke at 3 months. (Table 3).

Table:3 Predictors Of Poor Mrs Score Post Stroke

VARIABLES		MRS SCORE		P value
		<3	>3	
AGE GROUP	<65	63	4	0.022
	>66	26	7	
SEX	MALE	59	7	0.861
	FEMALE	30	4	
HYPERTENSION	NO	46	4	0.338
	YES	43	7	
CHOLESTEROL	NO	69	11	0.079
	YES	20	0	
DYSLIPIDEMIA	NO	68	9	0.687
	YES	21	2	
DIABETES	NO	49	7	0.589
	YES	40	4	
SMOKING	NO	65	10	0.196
	YES	24	1	
ALCOHOL	NO	61	8	0.777
	YES	28	3	
NIHSS SCORE AT ADMISSION	<4	39	1	0.006
	5-15	41	8	
	16-20	9	1	
	>21	0	1	
LEUKOARAIOSIS	GRADE 1	22	0	<0.0001
	GRADE 2	23	0	
	GRADE 3	10	9	
	NO	34	2	

DISCUSSION

The reported prevalence of leukoaraiosis in stroke patients varies among studies, from 6.8% to 44.4% [6, 7,8]. This variability may due to the differences in demographic characteristics among study populations including age, race, ethnicity and imaging protocols. Prevalence in our study is 64% which is higher compared to previous studies

It is well known that incidence of WMH(White matter hyperintensities) increases with age, especially in people over 60 years of age. Risk factors reported in various studies include female Sex, hypertension, heart disease, type 2 diabetes, abdominal obesity, hyperlipidemia, hyperhomocysteinemia , carotid stenosis, history of stroke, smoking, alcohol abuse, and chronic kidney disease, etc (.9,10) However, age, hypertension were consistently reported as major determinants of WMH. (11) We found severe WMH in 19% of our patients. Older patients more frequently had severe WMH.[12]

Few studies have reported a substantial proportion of younger patients also had severe WMH (18.0%)(13). Park, Anan, and Kocer et al., have shown that both low levels of HDL and hypertriglyceridemia may increase the risk of developing WMH (14). However, our study didn't show any correlation between dyslipidemia and LA similar to the study by Padovani and Streifler et al., (15) One recent study indicated that diabetes mellitus seems to be a risk factor for progression rather than new WMH development(16). Few studies have reported severe leukoaraiosis was associated with, hemorrhagic transformation after thrombolysis for ischemic stroke(17,18). our study didn't demonstrate significant hemorrhagic transformation in thrombolysed patients with severe leukoaraiosis

In our study, similar to previous studies, WMH was associated with age, and hypertension. However, it had no relation with hyperlipidemia, diabetes mellitus, smoking, and obesity. In most previously reported studies, Leukoaraiosis was strongly associated with lacunar strokes rather than non-lacunar, territorial strokes [19]. In addition, an inverse correlation between high-grade (> 50%) stenoses of the extracranial arteries and white matter changes have been reported [20). However, our study didn't find any association between various stroke types and leucoaraiosis.

We demonstrated that severe WMH was an independent predictor of short-term outcomes in stroke patients as evidenced by poor MRS score at 3 months. These findings were consistent with other reported studies[21]. Poor short-term outcomes in stroke patients with severe WMH may lead to higher long-term mortality

Various mechanisms underlying the influence of WMH on short-term functional outcomes were postulated. WMH regions have reduced vascular density and cerebral blood flow, which may lead to infarct growth after ischemic events during the acute period. The presence of dysfunctional neuronal connectivity in patients with WMH may result in decreased functional connectivity of distant cortical regions which could impair plasticity and inhibit recovery This may result in decreased functional connectivity between distant cortical regions [22]

As WMH is closely associated with cognitive dysfunction, post-stroke depression, decreased motivation, and poor cooperation during rehabilitation, it may have an additive effect on poor post-stroke outcomes (23). It has been hypothesized that in patients with chronic white matter injury, even small strokes/infarct volume could result in relatively severe deficits related to impaired brain plasticity.[24,25]. Smaller-sized infarcts produced the same deficit severity in patients

with severe leukoaraiosis as a larger infarct in patients with only none-to-mild leukoaraiosis (26)

We also found that the degree of initial neurological deficit severity as assessed by the admission NIHSS and age were also predictors of poor stroke outcome as evidenced by the 90-day MRS score. A Milder NIHSS score of less than 6 has a more favorable clinical outcome at 3 months as compared with other published consecutive stroke cohorts[27].

Strength And Limitations

Strengths of our study include prospective data collection and blinded assessment of neuroimaging variables. The Major Limitation of our study is the small sample size. Confounding effects such as stroke volume, post-stroke infection, and dementia which may contribute to post-stroke outcome were not studied.

CONCLUSION

Our results revealed, severe leukoaraiosis independently correlates with poor neurological deficit recovery after an ischemic stroke. Hence therapies that slow the progression of leukoariosis will reduce the incidence and severity of stroke as well as improves the clinical outcomes post-stroke. As leukoaraiosis have a significant impact on individual and the healthcare system, it is crucial to understand the risk factors for Leukoaraiosis and its prevention and treatment strategies

Further studies are required to establish the contribution of leukoaraiosis to functional outcomes after minor ischemic stroke beyond its impact on recovery mechanisms

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