

Saint Paul's Hospital Millennium Medical College



A thesis Submitted to the Department of Radiology Presented in Partial
Fulfillment of the Requirements for the certificate of specialty in
Radiology

**MAGNITUDE, DEGREE AND RISK FACTORS OF LEUKOARAIOSIS
AMONG AGE ABOVE 40 YEARS OLD BRAIN MRI IMAGED
PATIENTS AT SAINT PAUL'S HOSPITAL MILLENNIUM MEDICAL
COLLEGE, ADDIS ABABA, ETHIOPIA, 2019**

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Acronyms

AOR= Adjusted Odds Ratio
ARWMC=Age Related White Matter Changes
CKD=Chronic Kidney Disease
CR=Continuous Radiation
CVD=Cardiovascular Disease
DM=Diabetes Mellitus
DX=Digital X-ray
FLAIR=Fluid Attenuation Inversion Recovery
GFR=Glomerular Filtration Rate
HTN =Hypertension
LA= Leukoaraiosis
MDCT=Multi Detector Computerized Tomography
MMSE=Min Mental State scale
MRI= Magnetic Resonance Imaging
PACS= Picture Archiving and Communication System
PI=Principal Investigator
RIS= Radiology Information System
SPHMMC=Saint Paul's Hospital Millennium Medical College
WMC = White Matter Changes
WMH=White Matter Hyperintensities
WML =White Matter Lesions

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ABSTRACT

Background: Leukoaraiosis (LA), also known as white matter lesions (WMLs), is age-related white matter changes (WMC) which is considered as manifestation of arteriosclerotic small vessel disease and are related to age and vascular risk factors. Leukoaraiosis seems asymptomatic but it is not benign. Some reports also showed that Leukoaraiosis could coexist with other geriatric disorders. In Ethiopia, there is scarcity of evidence on magnitude and degree of Leukoaraiosis or investigation of risk factors for Leukoaraiosis had found being the problem frequently seen in our clinical practice.

Objective: The aim of this study was to determine Magnitude, degree and associated factors of white matter changes (WMC) among age above 40 years old brain MRI imaged patients at Saint Paul's Hospital Millennium Medical College (SPHMMC) radiology department from September, 01, 2018 to December /31/2018.

Methods: A Hospital based retrospective cross –sectional study was conducted on 102 Brain MRI imaged age above 40 years old patients. Data was collected by using data abstraction tool in the radiology department from medical record (card and PACS). The data was analyzed using SPSS version 20.

Time and budget plan: The study was conducted from April to August 2019 with estimated grand total budget of 25,500 birr.

Results: From a total of 102 subjects 94(92.4%) have some degree of MRI FLAIR cortical hyper intensities, from this 57(60.6%) have asymmetric distribution whereas 37(39.4%) have symmetrical distribution. The majority 85(92%) involved both deep subcortical and periventricular white matters and 52.9% had mild LA (52.4% were men, 47.9% were women) and 21.4% had moderate and 26.6 severe LA (50.1% were men, 49.9% were women).

Majority of subjects 78.4% of age from 40 to 49 have no Global cortical atrophy whereas 80% (30% mild, 50% moderate or severe) subjects age above 70 years have some degree of global cortical atrophy. Similarly, subjects 82.4% of age from 40 to 49 have no Parietal cortical atrophy whereas 80% subjects age above 70 years have some degree of Parietal cortical atrophy and 90% of age above 70 subjects have some degree of medial temporal lobe atrophy.

Conclusions: This study highlighted the high incidence of LA in hospitalized patients in Ethiopia and confirmed age and hypertension as the most important risk factors for LA. In the present study, we revealed that LA was a complex illness that may be driven by multiple vascular factors, including diabetes. The identification and further confirmation of those factors for overall LA risk, LA occurrence, and LA progression could provide effective information for clinicians and scientists to explore effective strategies for the prevention and treatment of LA.

Introduction

Back ground

Leukoaraiosis was first described 30 years ago. The term was originally coined by Hachinski in 1987 (leuko – white, araiosis – rarefaction) [1,2]. Leukoaraiosis, also known as white matter lesions (WMLs), is a universal neuroimaging phenomenon that often occurs in elderly people [1,2]. It refers to white matter Hyperintensities (WMHs) that are observed on magnetic resonance imaging (MRI) of the brain on T2-weighted and fluid-attenuated inversion recovery(FLAIR) sequences [3,4].

According to MRI features, WMLs are classified as periventricular WMLs and deep/subcortical WMLs. Periventricular WMLs include the smooth caps around the frontal horns and the line-like and halo-like lesions along the bodies of the lateral ventricles [5,6].

Deep/subcortical WMLs, however, include punctuate or confluent lesions that are distant from the lateral ventricle. Different types of WMLs may have varying pathogeneses [5,6,7].

LA is even considered as an important MRI marker for cerebral small vessel disease progression [8]. However, the pathogenesis of Leukoaraiosis remains unclear to date and it has long been debated. The pathological features of periventricular WMLs support their origin in ependymal layer damage, while the anatomical features of the periventricular white matter arterial blood supply support their origin from ischemia [8].

Thus, periventricular WMLs may be attributable to both ischemia and the ependymal layer, while most studies on subcortical WMLs support long-term chronic ischemia as the cause. Hence, more research is needed to determine whether different types of WMLs have varying pathogeneses [8].

During the past 20years, several epidemiological investigations on have Leukoaraiosis been performed in Australia, Europe, Asia and America [9–14]. The prevalence of Leukoaraiosis is high in certain populations, and it increases with age [9,14,15]. Studies in healthy community-based populations have demonstrated that the prevalence of Leukoaraiosis increased from 50.9% in healthy persons aged 44 to 48 years to 95% in healthy persons aged 60 to 90 years [9,10].

Statement of the problem

Leukoaraiosis seems asymptomatic but it is not benign. Some reports also showed that Leukoaraiosis could coexist with other geriatric disorders, such as dementia, Alzheimer disease, Parkinson disease, and stroke [4,15]. With the improvement in neuroimaging technology and the widespread use of MRI in the diagnosis of central nervous system disorders, that prevalence of Leukoaraiosis is increasing rapidly in the worldwide [4,15].

Moreover, Leukoaraiosis has been confirmed to be associated with an increased risk of dementia, stroke, brain atrophy, abnormal gait, and urinary incontinence, [15–18] which could lead to disability, worse stroke outcome, poor quality of life, and high health care costs [15,19].

Moreover, Leukoaraiosis is increasingly becoming a major public health challenge with the growth of the aging population. Therefore, exploring the comprehensive epidemiology of Leukoaraiosis and screening for its clinical risk factors are required for the understanding, prevention, and management of Leukoaraiosis. In Ethiopia, to the investigator knowledge, so far no published study on magnitude and degree of Leukoaraiosis or investigation of risk factors for Leukoaraiosis had done, but the problem frequently seen in clinical practice.

Significance of the study

This study can provide a picture understanding of Leukoaraiosis brain MRI imaged patients in Ethiopia; determine the effects of age, sex, education, hypertension, diabetes, cardiovascular disease, CKD and dyslipidemia, and epigenetic factors, such as smoking and drinking, on the risk and severity of Leukoaraiosis; and identify those risk factors as potential biomarkers for the diagnosis and management of Leukoaraiosis.

Literature review

Cohort Study with 3360 participants done at 2001 in Massachusetts, Boston, USA on alcohol consumption and brain MRI findings indicated U- shaped relation between alcohol consumption and age related white matter changes. Moderate alcohol consumption is associated with low prevalence of White matter changes and infarcts, thought to be vascular origin but dose-dependent brain atrophy [20, 21].

A community based study done in Washington, Seattle USA at 1996 with sample size of 3301 participants with symptomatic small vessel disease in elderly people on assessment of medical risk factors for age related white matter lesions revealed significant association with age, silent stroke and hypertension [12,13,22].

A cohort study done in age above 60 years' patients with at least 10 years' duration of HTN at 2013 in Hashimoto Japan on Major risk factors for the appearance of white-matter lesions on MRI in hypertensive patients with controlled blood pressure demonstrated WMLs in patients with well-controlled BP were not found to be associated with either the central aortic blood pressure or the brachial blood pressure. Patients with lower eGFR values showed more marked progression of the WMLs than those with a higher eGFR. As to the sites of the WMLs, lesions in the frontal and parietal areas with prominent sclerotic changes of the medullary arteries were more advanced in the patients with lower eGFR values than in those with higher eGFR [15,23,24,25].

A 3-year Longitudinal cohort study with 99 subjects with symptomatic small vessel disease done elderly people in London UK revealed strong association between global brain atrophy and white matter lesions and regional variation in white matter progression [17].

A large study with well characterized population of normal people aged between 60 and 90 years with MR scanning in Scotland, UK at 2000, With carefully measured and rated the white matter lesions in the periventricular and subcortical regions in different brain regions, revealed Periventricular and subcortical white matter lesion load increased with age in men and women and in all regions of the brain [9,10].

Cohort retrospective study with 93 patients with mean age of 71 +/- 9 years done Italy at 2016 on relationship between diabetes and WMLs demonstrated strong longitudinal statistical correlation between diabetes and age related white matter changes [21,26].

A hospital-based cross-sectional study conducted on 2017 at Translational Medicine Research Center (TMRC), Xiamen University, China that included 4683 patients who were 40 years or older revealed; of the total subjects, 58.3% (2731/4683 cases) suffered from Leukoaraiosis. Leukoaraiosis was more frequent amongst elderly females, particularly in those older than 60, compared to men. The incidence of LA increased with age. Age, sex, hypertension, diabetes and smoking all were risk factors for Leukoaraiosis [27].

2010 Guangzhou, China study determined the severity of WMC for 172 patients with stroke on MRI by volumetric quantification and the ARWMC scale. The study showed that the ARWMC scale correlated with cognitive performances. The correlation between ARWMC scale and cognition remained robust even adjusted for other clinical variables. They found that the various WMC measures correlated with both executive function and global cognition. Although some studies suggested that WMC selectively impair executive function and psychomotor speed [28,29], other studies of larger sample size or that included subjects with more severe WMC showed that WMC severity correlated not only with executive function but also with global cognition as well [4,9,10].

Study done in India in 2015 demonstrated white matter lesions are associated with late life depression and in post stroke patients severe DWMCs predicts post stroke depression [29,30].

OBJECTIVES

General objective

- ✓ To determine magnitude, degree and risk factors of Leukoaraiosis among age above 40 years old brain MRI imaged patients at Saint Paul's Hospital Millennium Medical College from September, 01, 2018 to December /31/2018

Specific objectives

- ✓ To determine magnitude of Leukoaraiosis
- ✓ To determine degree of Leukoaraiosis
- ✓ To identify risk factors of Leukoaraiosis

Methods and Materials

Study area and study period

Study Area

The study was conducted at department of radiology, SPHMMC in Addis Ababa, Ethiopia.

St. Paul's Hospital was built in 1961 by Emperor Haile Selassie in collaboration with the German Evangelical Church, as a source of medical care for underserved populations. It's the number one well equipped hospital in the country with modern 1.5 tesla MRI scanner, 64 slice MDCT, numerous modern ultrasound machines, modern Fluoroscopy DX and CR machines, mammography and interventional radiology equipments.

Department of radiology is one of the leading in radiology service in Ethiopia and patients from throughout the country imaged with affordable cost compared with private imaging centers and it is capable of giving services for 24 hrs./ day.

Study Period

September 01, 2018 to December 31, 2018

Study Design

Hospital based analytical cross-sectional study was used to determine magnitude, degree and factors associated with Leukoaraiosis.

Study Population

All age above 40 years old brain MRI imaged patients in SPHMMC from September 2018 to December 2018.

Inclusion Criteria

All age above 40 years old brain MRI imaged patients in SPHMMC from September 2018 to December 2018.

Exclusion Criteria

Patients with intracranial space occupying lesions.

Patients with specific white matter lesion pattern

Sample Size Determination

The Sample Size using single population proportion formula is calculated as follows

$n = z^2 \frac{p(1-P)}{d^2}$ where n = sample size, z = confidence interval,
 p = estimate of proportion, d = margin of error

P=50% (According to investigator search, there is scarcity of study in similar setting, so p value of 50% and marginal error of 5% are taken)

Z=1.96 , D=0.05

The calculated sample size is 384. Assuming 10% non-response rate, a total of 422 study subjects are required but, because of short study time, investigator studied all the subjects from September 1,2018 to December 31,2018(those have complete PACS data), that is 102 subjects .

Data Collection and analysis

Data collection tool and Procedure

This survey is a hospital population based, cross sectional, retrospective study conducted in St Paul's hospital millennium medical college, Addis Ababa, Ethiopia. The flow of subject recruitment for the study population is shown in the Figure 1. This study followed 246 subjects who were brain MRI imaged from September 2018 to December 2018. The inclusion criteria included a total of 246 subjects, all above 40 years of age and 106 subjects were excluded by exclusion criteria (subjects with intracranial space occupying lesions and Patients with specific white matter lesion pattern) that could hinder interpretation of white matter lesions. The remaining 38 subjects were excluded because of lack of MRI data and sufficient medical record.

After the exclusion 38 subjects whose brain FLAIR-MRI information or medical record was missing and 106 subjects who were diagnosed with intracranial space occupying lesions (tumor, hemorrhage, infection etc.) and Patients with specific white matter lesion (MS, ADEM, PMLE etc.) as described in exclusion criteria, a total of 102 subjects were included in the final analysis.

Data collection and evaluation

We collected the clinical data, including sex, age, and the diagnosis of hypertension, cardiovascular disease, CKD, diabetes, current neuropsychiatric diagnosis, smoking and drinking status from medical record, and the results of the FLAIR-MRI of the brain from PACS.

The enrolled patients were older than 40 years, and they were divided into 4 groups according to age: 40 to 49, 50 to 59, and 60 to 69 and above 70 years old. Hypertension was considered a systolic Blood pressure=140mmHg and/or a diastolic blood pressure=90 mm Hg according to the 1999 World Health Organization (WHO) hypertension. Guidelines for the prevention and treatment of

Diabetes was determined as a fasting glucose level=7.0mmol/L or 2-hour post glucose load glucose levels=11.1mmol/L, according diabetes.to the diagnostic criteria of WHO for

Cigarette smoking was defined as having smoked at least 10 cigarettes daily for at least 2 years. Drinking was defined as having a history of chronic alcoholism for 10 years. The LDL-C level

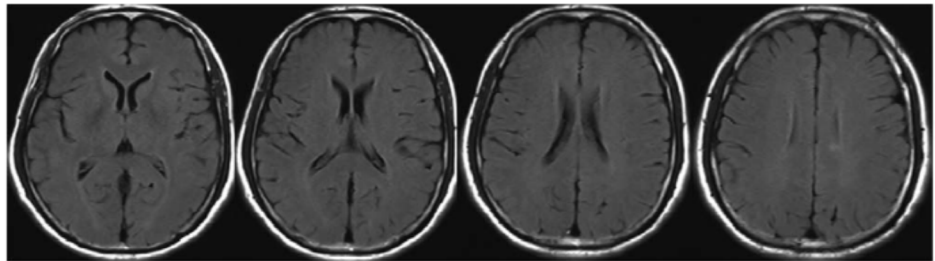
was divided into 3 groups: <2.07mmol/L, =2.07mmol/L and 3.36mmol/L and 3.36mmol/L. The normal LDL-C level was considered to vary > from 2.07 to 3.36mmol/L, which are adopted from the guide lines St Paul's hospital practicing.

MRI of the brain was performed using 1.5Tesla scanner and the MRI protocol included T1, T2-weighted images, SWI and axial FLAIR.

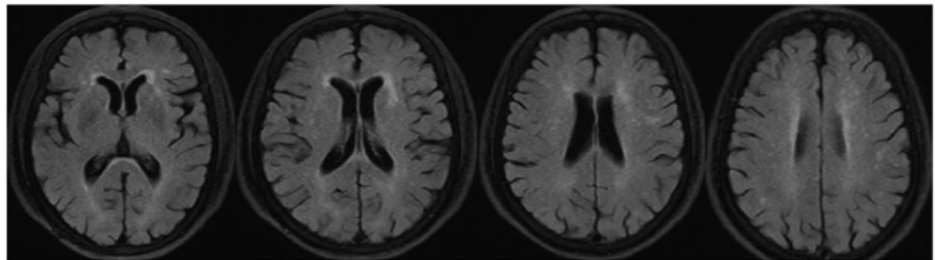
LA was defined as cerebral WMLs detected by the T2 and FLAIR MRI technology using 1.5 T scanners. According to the Fazekas scale, LA is often divided into 2 broad categories: periventricular WMLs and deep/subcortical WMLs.

Given that LA shows heterogeneous forms of WMLs that could reflect different progression states and clinical consequences, we moreover divided LA into 3 groups, "mild LA," showing punctate foci and/or "caps" or pencil-thin lining; "moderate LA," showing beginning confluence of foci and/or smooth "halo," and "severe LA," showing large confluent abnormalities,

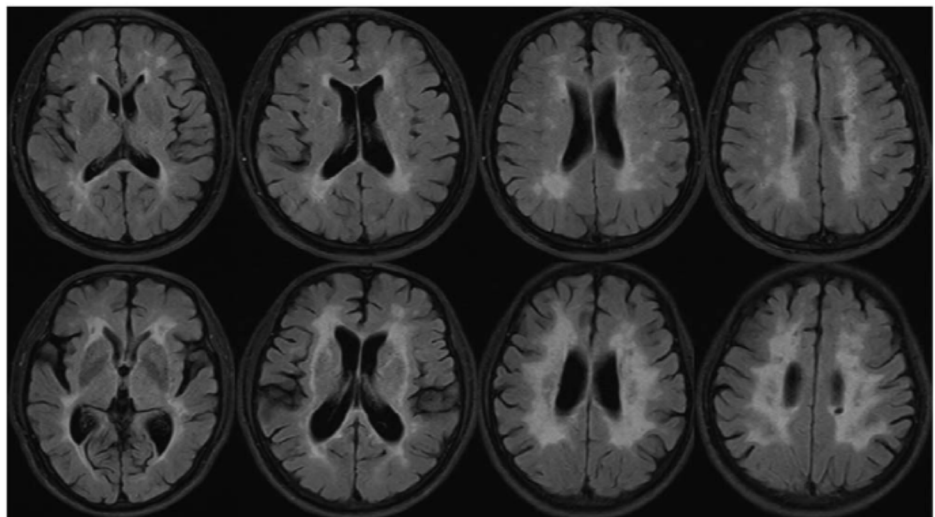
Normal



Mild LA



Moderate and Severe LA



according to the severity of the WMLs.

Normal was defined as the absence of cerebral WMH signals on the several sections of the FLAIR MRI scans. Both an experienced radiologist and training radiology residents who was blinded to all clinical information independently assessed the neuroimaging and then two readings were compared to reach a consensus during the analysis of the MRI data.

The enrolled patients were then classified into “normal,” “mild LA,” and “moderate and severe LA” groups. The last group included those patients whose severity of LA ranged from “moderate” to “severe.” All 3 groups met the following criteria: ≥ 40 years of age and no changes or any degree of changes in cerebral subcortical white matter on the FLAIR MRI scans of the brain.

Statistical analyses

The categorical variables were expressed in numbers and percentages, and the continuous variables were expressed in mean values $\pm$ standard deviation (standard deviation) unless otherwise specified. We first used Pearson χ^2 test to compare the differences between the normal and the LA groups regarding sex, age, hypertension, diabetes, smoking, drinking, and dyslipidemia. Furthermore, the correlations of these variables were measured. All of the statistical analyses were performed using SPSS software version 20.0. All P values were calculated using a 2-sided test and a P value $< .05$ was considered statistically significant

Then, we used a multivariate logistic regression model to estimate odds ratio (OR) and corresponding 95% confidence intervals (CIs) for the association of the above factors with the overall LA risk, LA occurrence, and LA progression, respectively.

Study variables

Dependent variables

- ✓ Leukoaraiosis

Independent variables

- ✓ Age of the patient
- ✓ Sex of the patient
- ✓ Drinking Alcohol
- ✓ Smoking status
- ✓ Hypertension status
- ✓ Diabetes mellitus(DM) status
- ✓ Cardiovascular disease(CVD) status
- ✓ Chronic kidney disease(CKD) status

- ✓ Dyslipidemia status
- ✓ Dementia status
- ✓ Stroke status
- ✓ Depression status

Data Quality Assurance

The data abstraction tool was used to collect data after being pre-tested before the study period. Modification of the abstraction tool was done based on the pre-test. The data collectors were trained on the abstraction tool, all of the collected data was reviewed and checked for completeness and relevance by the principal investigator and continuous supervision was arranged to control the data collection procedure. Further, data cleaning was performed to check for outliers, missed values and any inconsistencies before the data were analyzed using the software.

Ethical Consideration

Ethical clearance was obtained from the radiology department research board and St Paul's hospital IRB to use MRI image and medical charts of the patients. The patient data including the radiologic and epidemiological data were anonymized during data entry, analysis and dissemination of the report.

Dissemination Plan

The results of the research will be presented to department of radiology. Findings will also be presented on different conferences and professional society meetings. The findings will also be published in a relevant scientific journal.

Results

Amongst 102 subjects, 52 (51. %) were male and 50(49%) were female, the age range were from 40 to 92 years old (33.3%, 35.3%, 21.6% and 9.8% were 40–49, 50–59,60-69 and above70 years old, respectively). The mean age was 56.3 ± 9.5 years (57.1 ± 9.8 years for men and 56.2 ± 8.3 years for women).

The majority of the subjects did not have a history of diabetes (94.1%), smoking (97.4%), or drinking (91.0%). Amongst all of the subjects, 42(41.2%) suffered from hypertension, 26(25%) have cardiac disease and 29 (28.4%) showed abnormal lipid profile and 21(20%) have history of stroke. However, only 6 (5.9%) and 7(6.9%) have depression and cognitive disorder respectively.

From a total of 102 subjects 94(92.4%) have some degree of MRI FLAIR cortical Hyperintensities, from this 57(60.6%) have asymmetric distribution whereas 37(39.4%) have symmetrical distribution. The majority 85(92%) involved both deep subcortical and periventricular white matters and 52.9% had mild LA (52.4% were men, 47.9% were women) and 21.4% had moderate and 26.6 severe LA (50.1% were men, 49.9% were women).

Majority of subjects 78.4% of age from 40 to 49 have no Global cortical atrophy whereas 80% (30% mild,50% moderate or severe) subjects age above 70 years have some degree of global cortical atrophy. Similarly, subjects 82.4% of age from 40 to 49 have no Parietal cortical atrophy whereas 80% subjects age above 70 years have some degree of Parietal cortical atrophy and 90% of age above 70 subjects have some degree of medial temporal lobe atrophy.

Micro bleeds in Susceptibility weighted imaging are noted only 4(3.9%) of subjects, all are lobar in location and 75% seen in hypertensive subjects and all are seen in age above 70 years old subjects.

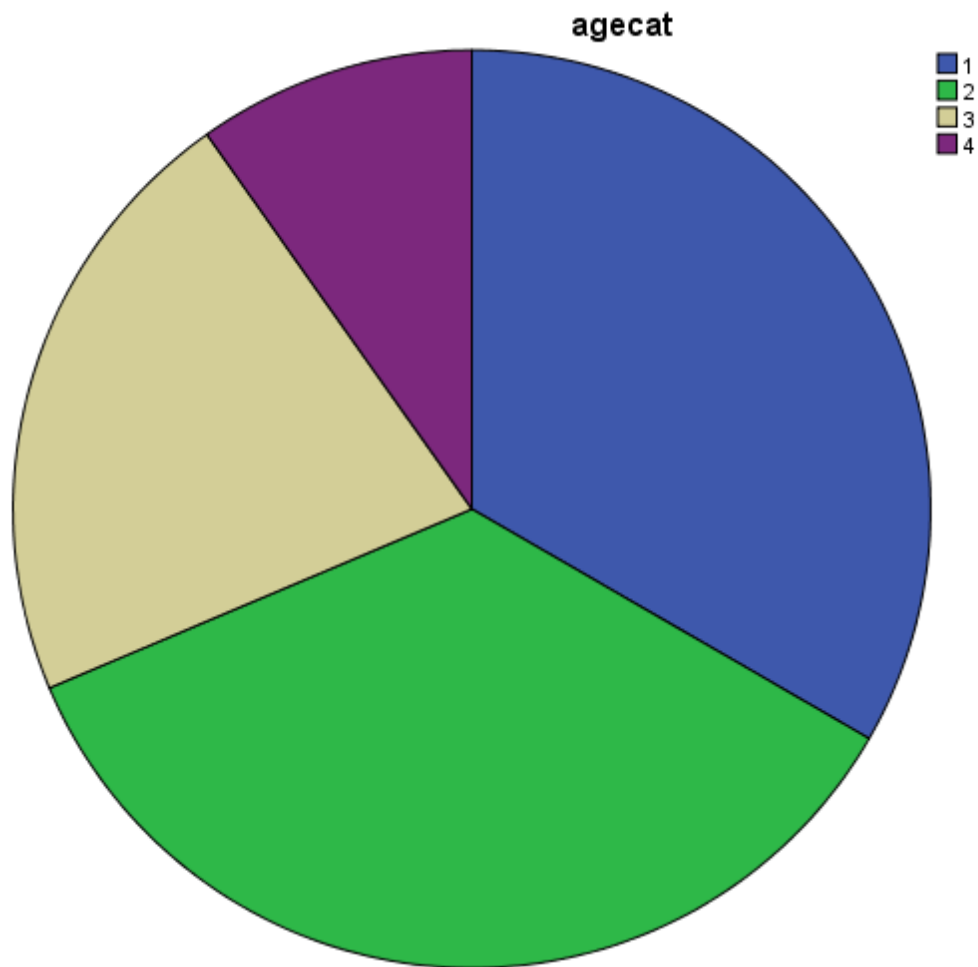
Table:1 frequency table for independent variables

Variables	Frequency	Percent	Valid Percent	Cumulative Percent
Age category				
40-49	34	33.3	33.3	33.3
50-59	36	35.3	35.3	68.6
60-69	22	21.6	21.6	90.2
Above 70	10	9.8	9.8	100.0
sex				
Male	52	51.0	51.0	51.0
Female	50	49.0	49.0	100.0
alcohol status				
No	93	91.2	91.2	91.2
Yes	9	8.8	8.8	100.0
Smoking status				
No	99	97.1	97.1	97.1
Yes	3	2.9	2.9	100.0
Hypertension				
No	60	58.8	58.8	58.8
Yes	42	41.2	41.2	100.0
Diabetes				
No	96	94.1	94.1	94.1
Yes	6	5.9	5.9	100.0
CVD				
No	76	74.5	74.5	74.5
Yes	26	25.5	25.5	100.0
Cognitive disorders				
No	95	93.1	93.1	93.1
Yes	7	6.9	6.9	100.0
Dyslipidemia				
No	73	71.6	71.6	71.6
Yes	29	28.4	28.4	100.0
Depression History				
No	96	94.1	94.1	94.1
Yes	6	5.9	5.9	100.0
History of stroke				
No	81	79.4	79.4	79.4Y
Yes	21	20.6	20.6	100.0

Crosstab

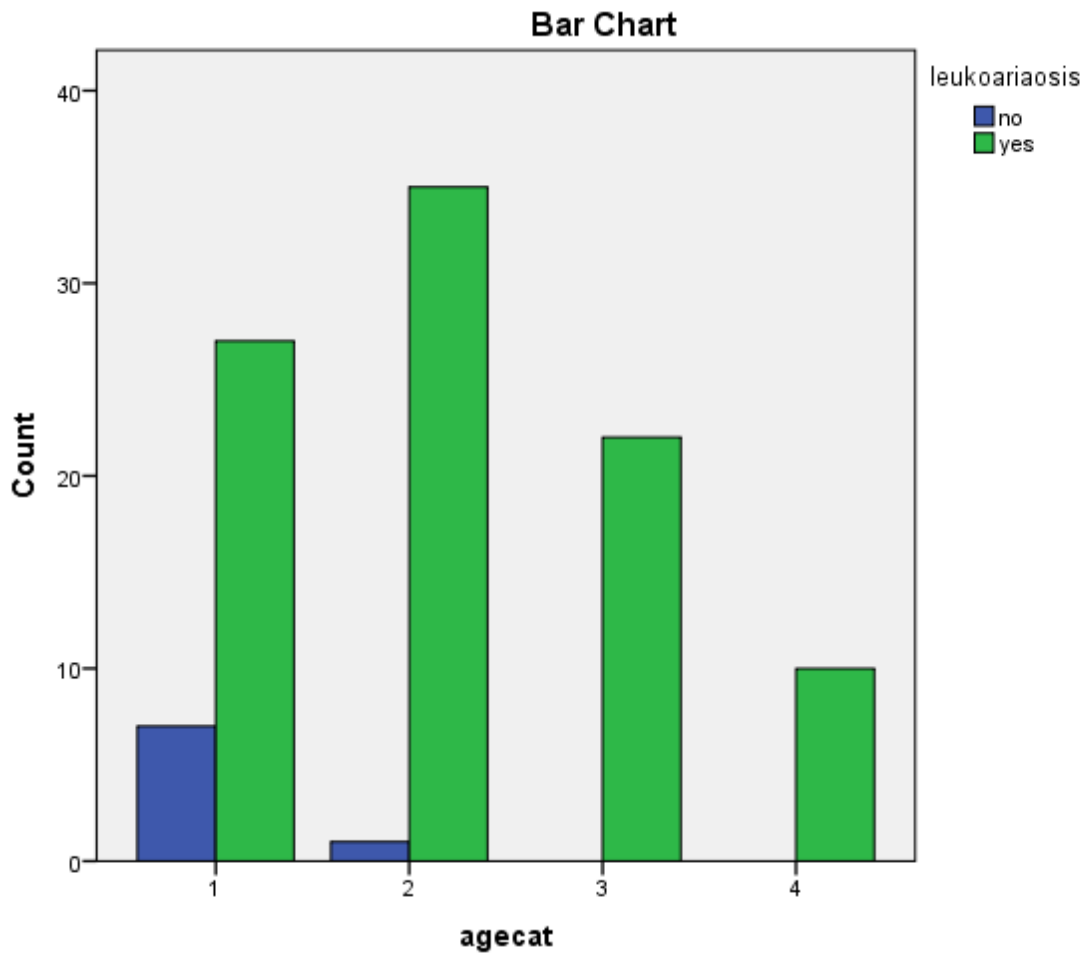
			leukoariaosis		Total
			no	yes	
Age catagory	1	Count	7	27	34
		Expected Count	2.7	31.3	34.0
		% within agecat	20.6%	79.4%	100.0%
	2	Count	1	35	36
		Expected Count	2.8	33.2	36.0
		% within agecat	2.8%	97.2%	100.0%
	3	Count	0	22	22
		Expected Count	1.7	20.3	22.0
		% within agecat	0.0%	100.0%	100.0%
	4	Count	0	10	10
		Expected Count	.8	9.2	10.0
		% within agecat	0.0%	100.0%	100.0%
	Total	Count	8	94	102
		Expected Count	8.0	94.0	102.0
		% within agecat	7.8%	92.2%	100.0%

Table: 2 showing the frequency of LA among different age category (where age category 1 from 40-49,2; 50-59; 3 from 60-69 and 4 above 70 years of age)



Fig;2 pie chart of age category

Key: age category 1 from 40-49; 2 from 50-59; 3 from 60-69 and 4 above 70 years of age)



Fig;3 Bar chart of age category

Key: age category (1 from 40-49; 2 from 50-59; 3 from 60-69 and 4 above 70 years of age)

Prevalence of LA in males and females.

The overall magnitude of LA was 92.4% in the total subjects (94 of 102 cases), 52.1 % (49) in men and 47.8 % (45) in women.

Of all the LA subjects, and 52.9% had mild LA (52.4% were men, 47.9% were women) and 21.4% had moderate and 26.6 severe LA (50.1% were men, 49.9% were women).

The magnitude of LA Increased with age amongst men and women and peaked in the age group above 70 years old for both men and women. The prevalence of LA was 79.4 %in those aged 40 to 49 years, 97.2%in those aged 50 to 59 years, 100% in those aged above 70 years' old

Risk factors for LA

To identify the risk factors for LA, we first evaluated the associations of sex, age, hypertension, diabetes, smoking, drinking and dyslipidemia with LA risk using the x2 test.

Among the variables significantly associated with LA were age, hypertension, alcohol history and diabetes ($P<.005$). The significant risk factors were age ($P<.001$) and hypertension ($P<.002$). The prevalence of overall LA, mild LA, and moderate and severe LA all increased with age, indicating that age not only acts as a crucial risk factor for LA but also has an important effect on the severity of LA. Furthermore, we stratified by age for those categories of the 4 significantly associated factors described above. As expected, the age-specific prevalence of overall LA increased with increasing age within each category.

Table:2 hypertensive * Leukoaraiosis

Crosstab					
			Leukoaraiosis		Total
			no	yes	
hypertensive	No	Count	8	52	60
		Expected Count	4.7	55.3	60.0
		% within hypertensive	13.3%	86.7%	100.0%
	Yes	Count	0	42	42
		Expected Count	3.3	38.7	42.0
		% within hypertensive	0.0%	100.0%	100.0%
Total	Count		8	94	102
	Expected Count		8.0	94.0	102.0
	% within hypertensive		7.8%	92.2%	100.0%

Discussion

In the present study, we reported a high incidence of LA. The incidence of LA in our subjects (92.4%) was higher than that reported in Chinese hospitalized patients (58.3%rate), [18] and also higher than those observed in healthy populations from the Netherlands, [5] Australia, [21] and Europe, [7] respectively. Age range, comorbid medical disorders, ethnicity, and sample sizes likely account for the between-study differences in LA incidence.

In addition, our study showed that the overall incidence and severity of LA gradually increased with age, with a similar pattern in men and women, in accordance with previous studies. These results support age as the crucial risk factor for LA.

This present study showed that the incidences of overall LA, mild LA, and moderate and severe LA were similar in women and men; we found that both sexes had similar contributions from factors such as hypertension, diabetes, and dyslipidemia in the association analysis opposing to previous study suggesting women, particularly older subjects (>60 years old), are predisposed to LA than men [5,11]. Physiological causes (such as hormone levels, brain morphology, etc.) and/or genetic factors may contribute to the sex difference. [25,26]. Small sample size may explain the difference in the result.

In addition to the age, the present study also confirmed the close association between hypertension, diabetes, alcohol status and LA through both single-factor analysis and multivariate logistic analysis. Consistent with previous results, [27–29] our findings identified hypertension as the most important risk factor for LA. Although the roles of hypertension in LA remain unclear, we think that they may be associated with the pathology of LA, such as widespread perivascular rarefaction of myelin, patchy demyelination, partial loss of axons and oligodendroglial cells, mild reactive astrocytic gliosis, and sparsely distributed macrophages and the disruption of endymal. [4,30]

In according with the significant association of hypertension with overall LA, we found that the incidence of LA in the group with diabetes was significantly higher than that in the group without diabetes at each age category. Consistent with the recent finding, [31] this suggests that diabetes is an important risk factor for LA.

However, smoking and LDL-C levels may not contribute to the occurrence of LA, but they may contribute to its progression. We thought that the lack of a significant association between smoking and LDL-C with the overall LA observed in both the single-factor analysis and development.

Taken together, the above results indicate that LA is not a typical type of neurodegenerative disease but is an avoidable disease, and controlling certain vascular risk factors could be helpful for patients to prevent LA occurrence and slow down LA progression.

To date, the effect of antihypertensive medication on LA progression has been confirmed by at least 3 large prospective population-based studies. [27–29] Those reports showed that ant

hypertension treatment was associated with a smaller increase in WML volume than no hypertensive treatment. Moreover, participants with poorly controlled hypertension had a higher risk of WMLs than those with successfully treated hypertension. Those findings suggested that the effective treatment of hypertension could reduce the risk of LA and prevent its progression. In addition to antihypertensive treatment, large longitudinal population-based studies are necessary to assess the role of antidiabetic treatment, smoking cessation, abstinent alcoholics, and controlling blood lipid levels with statins in the management of LA.

Although multiple putative mechanisms have been reported to be involved in the pathogenesis of LA, such as abnormal cerebral perfusion, dysfunction of the blood-brain barrier, ischemia damage, disturbances in cerebrospinal fluid circulation, diffuse cerebral microangiopathy, inflammatory response, and genetic changes,[32–41] an efficient management strategy has not been established to prevent the LA occurrence, slow down the disease progression or reverse already existing WMLs.[42] This study could provide an epidemiological evidence for making several specific interventions for the patients with different severity degree of LA,

Limitations

The major limitations of our study are the small sample size and short study period that hindered detailed evaluation of risk factors. Additional major shortcoming is that this is a hospitalized cross-sectional study in which there is almost certainly a selection bias. Therefore, the incidence in this study may not represent the overall incidence of LA in the general population. Moreover, we are unable to make inferences as to causality. Another potential limitation was the use of visual rating scales which may not only make the results of the study incomparable but may also result in an inexact assessment of LA incidence and progression. Therefore, an automated WMLs volumetric/quantitative analysis is suggested to be applied in the epidemiology study of LA in future. The last but not the least is the limitation that both the percent of subjects with stroke, CKD, CVD, depression and Cognitive disorders among this study cohort and the relationship of stroke and LA could not be assessed because the information is inaccessible for a large portion of subjects.

Conclusions

This study highlighted the high incidence of LA in hospitalized patients in Ethiopia and confirmed age and hypertension as the most important risk factors for LA. In the present study, we revealed that LA was a complex illness that may be driven by multiple vascular factors, including diabetes. The identification and further confirmation of those factors for overall LA risk, LA occurrence, and LA progression could provide effective information for clinicians and scientists to explore effective strategies for the prevention and treatment of LA.

Recommendations

Clinicians should focus on the prevention of LA as well as hinder progression by treating globally established risk factors like hypertension.

FMOH should create awareness among elderly to have screening for potential asymptomatic risk factors (HTN and DM) for LA.

Neuroradiologist should play role by providing early diagnosis and creating awareness among clinicians.

In the future, Community based large prospective studies should be conducted to determine all the risk factors of the LA and to confirm high incidence of LA in Ethiopia.

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Annex

Data abstraction tool for assessment of magnitude, degree and risk factors of Leukoaraiosis among age above 40 years old brain MRI imaged patients in St Paul's millennium medical college (to be fulfilled by medical professional)

Part I

Socio demographic factors, medical risk factors and current neuropsychiatric diagnosis

Date: ---/---/2019

Name -----MRN-----MRI No-----

Age-----years

Sex

- ☐ male
- ☐ female

Life style

- ☐ Alcoholic(Yes/No)
- ☐ Smoker (Yes/No)

Medical risk factors

- ☐ Hypertension
- ☐ Diabetes mellitus(DM)
- ☐ Cardiovascular disease(CVD)
- ☐ Chronic kidney disease(CKD)
- ☐ dyslipidemia

Current Neuropsychiatric diagnosis

- ☐ Dementia
- ☐ Seizure disorder
- ☐ Stroke
- ☐ Parkinson's disease
- ☐ Depression
- ☐ Others specify-----
- ☐ Part II

Brain MRI findings (to be read by professionals)

Is there T2 or FLAIR cerebral white matter hyperintensities? (yes/no), if yes

1. Symmetric/asymmetric
2. Location (frontal, occipital, parietal, temporal), infra tentorial
3. Types (subcortical or deep white matter/periventricular white matter lesions)
4. Degree (Fazekas scale)

For deep white matters

- 0: None or a single punctate WMH lesion
- 1: Multiple punctate lesions
- 2: Beginning confluency of lesions (bridging)
- 3: Large confluent lesions

For PVHs

- 0 = absence,
- 1 = 'caps' or pencil thin lining,
- 2 = smooth 'halo',
- 3 = irregular PVH extending into the deep white matter

Is there global cortical atrophy? (Yes/No), if yes GCA scale?

- 0: no cortical atrophy
- 1: mild atrophy: opening of sulci
- 2: moderate atrophy: volume loss of gyri
- 3: severe (end-stage) atrophy: 'knife blade' atrophy

Is there Medial Temporal Lobe Atrophy (yes/no) if yes MTA-scale?

- score 0: no atrophy
- score 1: only widening of choroid fissure
- score 2: also widening of temporal horn of lateral ventricle
- score 3: moderate loss of hippocampal volume (decrease in height)
- score 4: severe volume loss of hippocampus

Is there parietal lobe atrophy? (yes/No) if yes Koedam scale

- grade 0: closed sulci of parietal lobes and cuneus
- grade 1: mild widening of posterior cingulate and parieto-occipital sulci
- grade 2: substantial widening of parietal lobes
- grade 3: severe (end-stage) atrophy: 'knife blade' atrophy of parietal lobes

Is there enlarged perivascular spaces or etat cribre (yes/no) if yes location

- Basal ganglia/centrum semi ovale/mesencephalon/sub insular region

Is there micro bleeds (yes/No), if yes:

- Number (____) and location (lobar/ deep)

