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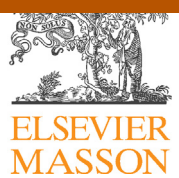

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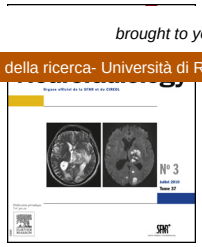

ORIGINAL ARTICLE

Is there an association between leukoaraiosis volume and diabetes?

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KEYWORDS
Leukoaraiosis;
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Summary
Objectives: The relation between white matter loss (WML) and diabetes is still debated. The aim of this study was to investigate the correlation between typical WML— and diabetes-related magnetic resonance imaging (MRI) findings in a cohort of patients scheduled for carotid endarterectomy (CEA).
Materials and methods: Ninety-three consecutive patients (mean age 71 ± 9 years; male 71) were included in a single-centre retrospective study. All the patients underwent MRI as baseline evaluation prior to CEA. A neuroradiologist blinded to the presence of risk factors calculated WML volume and number of lesions on FLAIR images using a semi-automated segmentation technique. Receiver operating characteristics analysis was performed to search for any association between WML volume and the number of WML lesions. The Mann—Whitney tests were used to determine significant WML differences between diabetic and non-diabetic patients. Logistic regression analysis was performed to evaluate the potential association of other variables.
Results: The prevalence of diabetes was 20.4% ($n = 19$). WML volume and number of WML lesions were significantly associated with diabetes ($P = 0.001$). A statistically significant difference in WML volume was found between diabetic and non-diabetic patients ($P < 0.0001$). Only diabetes, among all the investigated variables (WML volume, CAD status, age, smoking status, gender, hypertension, hyperlipidemia, diabetes) was significantly associated with WML ($P = 0.0001$).

Abbreviations: MRI, Magnetic resonance imaging; WML, White matter loss; CAD, Coronary artery disease; CEA, Carotid endarterectomy; ROC, Receiver operating characteristics; AUC, Area under the curve; DWI, Diffusion weighted imaging.

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Conclusion: Our results demonstrate a strong statistical correlation between diabetes and WML. Future scientific challenges could include the identification of potential therapeutic targets and the creation of dedicated screening protocols for WML in diabetic patients other than the simple measurement of leukoaraiosis total burden.

Introduction

Leukoaraiosis (LA) is a term coined by Hachinsky et al. [1] back in 1986 to define a diminution of representation of the white matter density; currently LA refers to the identification of areas of high signal intensities on T2-weighted and proton density sequences at magnetic resonance imaging (MRI), representing regions of scattered brain white matter loss (WML) associated with local increase in brain water content [2].

Despite numerous multi-centric studies published on the topic, the exact incidence of LA in the elder population remains unknown with current estimates varying greatly (5.3—95%) [3—5]. The cause of WML is not clear; it is probably related to low-grade vascular insufficiency (e.g. hypo-perfusion, arteriolar disease) leading to an atrophic perivascular demyelinization (corresponding to the histopathological findings of ischemic demyelinization and gliosis) [6]. Several studies have investigated the relationships between WML and various factors, including carotid plaque, age, stroke, hypertension, disability, cognitive decline, depression, gait and urinary disturbances [7—9]. Despite the supposed vascular etiology of WML, the precise relation with diabetes is still debated, since several authors reported quite discordant results on this association. Tiehuis et al. demonstrated that diabetic patients had more global and subcortical brain atrophy and larger WML lesions than matched non-diabetic patients [10]. Khan et al. confirmed a strong correlation between LA and diabetes in a large patient cohort [11]. On the contrary, other studies have not confirmed this association. Bogousslavsky et al. suggested that WML lesions are clearly correlated with hypertension, but not with diabetes [12]; van Harten et al. reported no association between diabetes and WML (OR 1.1 [95% CI 0.9—1.4]) in a cohort of patients with stroke or other cardiovascular risk factors and a mild association in the outpatient population [13]. The aim of the present study was to evaluate the association between diabetes and WML in a cohort of patients who underwent brain MRIs at our institution, in order to add further information to the current knowledge on the topic.

Materials and methods

Demography

Because of the retrospective nature of the study, the requirement for written informed consent was waived. Our cohort was composed of ninety-three consecutive patients (mean age 71 ± 9 years; male 71) scheduled for carotid endarterectomy (CEA) according to the NASCET and SPREAD guidelines [14—16]. Brain MRI was performed in all the patients as baseline evaluation before surgery. In this cohort of patients, only 32 were symptomatic (presenting with a history of transient ischemic attack or stroke or any neurological deficit occurring at least one month earlier) [16]. Considering the vascular risk factors, information about hypertension, diabetes, hyperlipidemia, previous medical history of coronary artery disease (CAD), and smoking habits were recorded for the entire study population. The evaluation of risk factors was performed in accordance with international guidelines, on the basis of clinical data and laboratory tests performed at baseline and/or considering previous medical records in patients on pharmacological treatment. Hypertension was defined as a blood pressure persistently at or above 140/90 mmHg. Diabetes was defined based on clinical history of two fasting glucose measurements above 126 mg/dL (7.0 mmol/L). Hyperlipidemia was defined as elevated plasma concentrations of any or all of the lipids.

We considered as exclusion criteria:

- other possible etiology for white matter disease, such as vasculitis, demyelinating disease and connective tissue diseases;
- previous pathologies, such as abscess, encephalitis or brain malignancy.

Brain MRI protocol and lesion assessment

Brain MRI examinations were performed using a Gyroscan 1.5-T superconducting magnet (Philips, Best, The Netherlands), with a head coil according to a standardized protocol. In each patient diffusion weighted imaging (DWI) was performed with a single-shot spin echo sequence with two diffusion-sensitivity values of 0 and 1000 s/mm^2 along the transverse axis. In addition to DWI sequences, axial and sagittal 2D FLAIR images (10,000/140/220 ms for TR/TE/TI; matrix 512 × 512; FOV: 240 × 240 mm^2; section thickness: 5 mm) were also obtained.

WML was identified from axial and sagittal FLAIR images by a neuroradiologist with 12 years of experience, blinded to the presence of risk factors; once the neuroradiologist identified the lesions, WML volume was automatically calculated using a semi-automated segmentation technique (Jim, Xinapse System, Leicester, UK). WML was defined as any hyperintense white matter region on FLAIR images not related to large vessel infarcts (Fig. 1). After the delineation of WML, its volume for each hemisphere, including both periventricular and deep subcortical lesions, was automatically calculated by the software, based on the slice thickness and outlined WML areas.

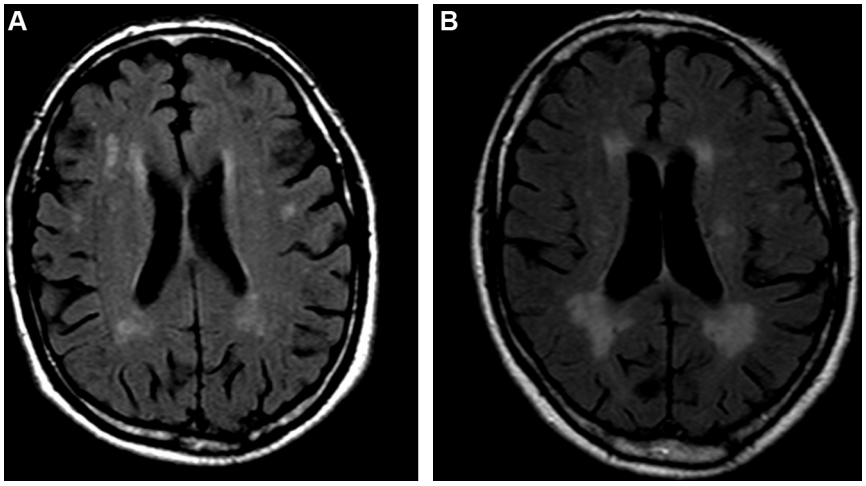

Figure 1 Male, 58 years old: FLAIR images showing WML in the periventricular white matter.

Statistical analysis

The normality of each continuous variable group was tested using the Kolmogorov—Smirnov *Z* test; appropriate tests for Gaussian or non-Gaussian values were selected. For Gaussian values, continuous data were described as the mean value ± SD whereas for non-Gaussian values, median values were given. The Mann—Whitney test was used to test the differences between the diabetic and non-diabetic patients.

Receiver operating characteristics (ROC) curve analysis was performed and the area under the curve (AUC) was calculated. Moreover thresholds of WML volume associated with presence of diabetes were derived. Stepwise logistic regression analysis was used to identify the most accurate linear combinations of cardiovascular risk factors. A *P*-value < 0.05 was regarded to indicate statistical significance association and all values were calculated using a two-tailed significance level. *R* software (www.r-project.org) was employed for statistical analyses.

Results

No patients were excluded from the analysis for suboptimal image quality and a total of 93 patients (mean age 71 ± 9 years; male 71, females 22) were included in the analysis. We found a prevalence of diabetes of 20.4%, with 19 patients being affected by type 2 diabetes. The onset of the type 2 diabetes was 54 ± 14 years. Among these 19 patients, the following complications were found: retinopathy ($n = 6$; 32%), nephropathy ($n = 5$; 26%), diabetic foot ($n = 3$; 16%). General demographic characteristics are summarized in Table 1.

ROC curve analysis

No patients were excluded from the analysis. The ROC curve analysis for WML volume versus the presence or absence of diabetes is given in Fig. 2a. General ROC results from the volume analysis are summarized in Table 2. The ROC—AUC (Az) showed a value of 0.812 (SE = 0.058 and 95% CI from 0.711 to 0.891), corresponding to a statistically significant association between diabetes mellitus and WML volume ($P = 0.001$).

The ROC curve analysis for the number of WML lesions versus the presence or absence of diabetes is given in Fig. 2b. ROC curve analysis for the association between diabetes and the number of white matter lesions is

Table 1 General demographic characteristics of the population.

Patient characteristics				
Parameter	Population	Diabetes	Non-diabetes	*P*-value
Patient (*n*)	93	19 (20.4%)	74 (79.6%)	NC
Age (years)	71 ± 9	69 ± 10	71 ± 9	0.285
Sex (male)	71 (76%)	15 (79%)	56 (76%)	0.764
Smoker	48 (52%)	7 (37%)	41 (55%)	0.148
Hypertension	62 (67%)	13 (68%)	49 (66%)	0.855
Coronary artery disease	51 (55%)	13 (68%)	38 (51%)	0.182
Ischemic event	53 (57%)	13 (68%)	40 (54%)	0.259
Dyslipidemia	51 (55%)	12 (63%)	39 (53%)	0.414
Statins and other drugs[a]	44 (47%)	10 (53%)	34 (46%)	0.603

[a] Other lipid lowering drugs.

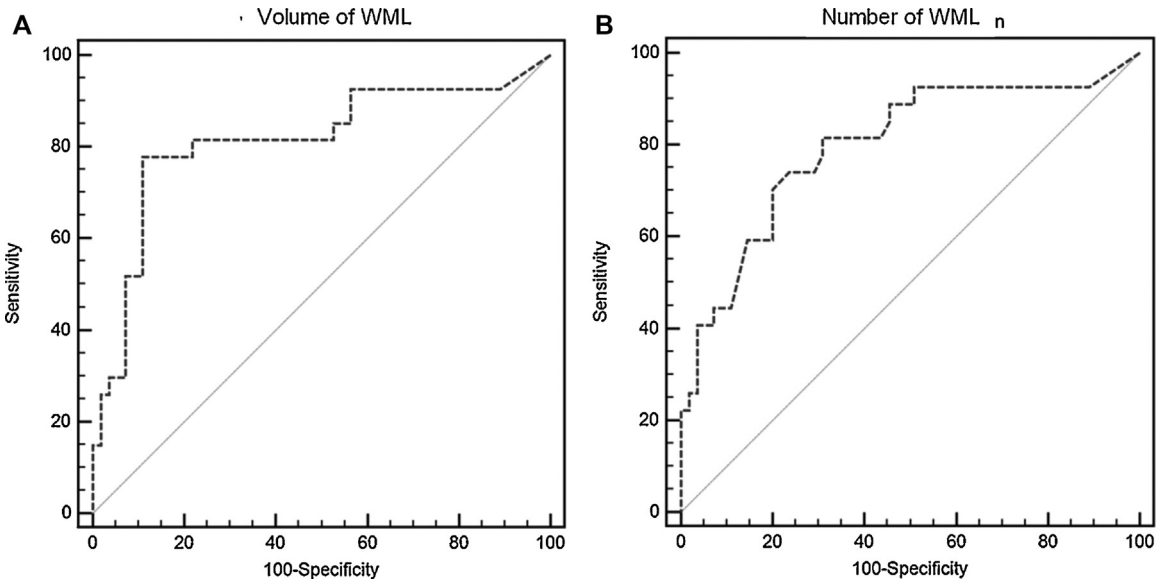

Figure 2 ROC curve analysis for WML volume and number of lesions versus the presence or absence of diabetes.

Table 2 ROC curve analysis derived table for the association between diabetes and WML volume.

Criterion (mm^3)	Sensitivity	95% CI	Specificity	95% CI	+LR	−LR
> 0	92.59	75.7—99.1	10.91	4.1—22.2	1.04	0.68
> 890	92.59	75.7—99.1	43.64	30.3—57.7	1.64	0.17
> 1215	85.19	66.3—95.8	43.64	30.3—57.7	1.51	0.34
> 1241	85.19	66.3—95.8	47.27	33.7—61.2	1.62	0.31
> 1250	81.48	61.9—93.7	47.27	33.7—61.2	1.55	0.39
> 2544	81.48	61.9—93.7	78.18	65.0—88.2	3.73	0.24
> 3068	77.78	57.7—91.4	78.18	65.0—88.2	3.56	0.28
> 3680	77.78	57.7—91.4	89.09	77.8—95.9	7.13	0.25
> 4916	51.85	31.9—71.3	89.09	77.8—95.9	4.75	0.54
> 5356	51.85	31.9—71.3	92.73	82.4—98.0	7.13	0.52
> 6523	29.63	13.8—50.2	92.73	82.4—98.0	4.07	0.76
> 7922	29.63	13.8—50.2	96.36	87.5—99.6	8.15	0.73
> 8350	25.93	11.1—46.3	96.36	87.5—99.6	7.13	0.77
> 8515	25.93	11.1—46.3	98.18	90.3—100.0	14.26	0.75
> 9530	14.81	4.2—33.7	98.18	90.3—100.0	8.15	0.87
> 11,541	14.81	4.2—33.7	100.00	93.5—100.0	NC	0.85
> 28,324	0.00	0.0—12.8	100.00	93.5—100.0	NC	1.00

summarized in Table 3. The ROC—AUC (Az) showed a value of 0.797 (SE = 0.056 and 95% CI from 0.696 to 0.878), with a *P*-value of 0.001.

Mann—Whitney test

The Mann—Whitney test analysis was also performed in order to compare the WML volume in patients with diabetes versus those without diabetes; a statistically significant difference was found with $P < 0.0001$. A statistically significant difference was found between the two groups also regarding the number of lesions ($P < 0.0001$). These data are summarized in Table 4 and Fig. 3a and b.

Logistic regression analysis

Stepwise logistic regression analysis was performed by creating a model with 7 variables: WML volume, CAD status, age, smoking status, gender, hypertension, hyperlipidemia. The model rejected all the variables with the exception of WML that showed a statistically significant association with diabetic status (Table 5).

Discussion

In the present study, we evaluated the presence and severity of WML disease in diabetic and non-diabetic subjects belonging to a cohort of patients scheduled for CEA, and we

Table 3 ROC curve analysis derived table for the association between diabetes and the number of WML lesions.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	−LR
≥ 0	100.00	87.2—100.0	0.00	0.0—6.5	1.00	NC
> 15	92.59	75.7—99.1	49.09	35.4—62.9	1.82	0.15
> 20	88.89	70.8—97.6	49.09	35.4—62.9	1.75	0.23
> 25	81.48	61.9—93.7	56.36	42.3—69.7	1.87	0.33
> 29	81.48	61.9—93.7	69.09	55.2—80.9	2.64	0.27
> 30	77.78	57.7—91.4	69.09	55.2—80.9	2.52	0.32
> 35	74.07	53.7—88.9	76.36	63.0—86.8	3.13	0.34
> 40	70.37	49.8—86.2	80.00	67.0—89.6	3.52	0.37
> 45	59.26	38.8—77.6	80.00	67.0—89.6	2.96	0.51
> 50	51.85	31.9—71.3	87.27	75.5—94.7	4.07	0.55
> 55	44.44	25.5—64.7	92.73	82.4—98.0	6.11	0.60
> 60	40.74	22.4—61.2	96.36	87.5—99.6	11.20	0.61
> 70	25.93	11.1—46.3	96.36	87.5—99.6	7.13	0.77
> 80	22.22	8.6—42.3	98.18	90.3—100.0	12.22	0.79
> 90	0.00	0.0—12.8	100.00	93.5—100.0	NC	1.00

Table 4 Mann—Whitney analysis for WML volume and number of WML lesions.

	WML volume	Number of WML lesions
Average rank of first group	33.0545	33.4727
Average rank of second group	58.7037	57.8519
Mann—Whitney U	278	301
Test statistic *Z* (corrected for ties)	4.585	4.358
Two-tailed probability	$P < 0.0001$	$P < 0.0001$

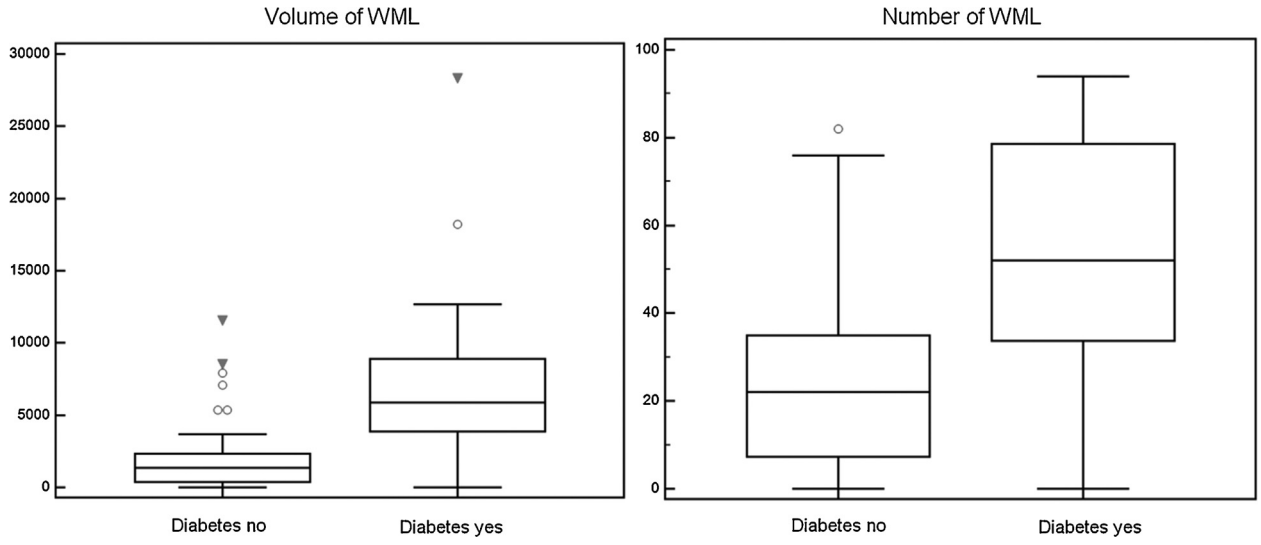

Figure 3 Mann—Whitney test analysis for WML volume and number of lesions in patients with diabetes versus those without diabetes.

demonstrated a statistically significant correlation between diabetes and LA, both in terms of number as well as of volume of WML lesions.

The pathogenesis of LA is partially unclear, but it is certainly related to chronic hypo-perfusion of neurons and glia cells, resulting in a complex cascade of intracellular alterations and in energy deficit [17]. Firstly, mitochondrial malfunction causes slight neuron and glia cell depolarization and altered intracellular pH, leading to further worsening of mitochondrial dysfunction [17]. Moreover, the prolonged ischemia determines dephosphorylation of the Tau protein-part of the microtubules system, determining further malfunctioning of the mitochondrial shuffle system. These cascades are enhanced in areas of higher O_2 deficit,

Table 5 Logistic regression analysis for WML volume.

Variable	Coefficient	Standard error	*P*	Odds ratio
WML volume	0.000391	0.0001016	0.0001	9.54
Age	—	—	> 0.05	NC
Sex (male)	—	—	> 0.05	1.21[a]
Smoker	—	—	> 0.05	0.47[a]
Hypertension	—	—	> 0.05	1.06[a]
Coronary artery disease	—	—	> 0.05	2.05[a]
Ischemic event	—	—	> 0.05	1.84[a]
Dyslipidemia	—	—	> 0.05	1.5[a]

[a] From the univariate analysis.

such as in the border zones, where the nuclei of the glia cells are usually located [17].

Many authors previously investigated the role of diabetes in brain pathology. Several studies reported a significant correlation between diabetes and WML and a few authors demonstrated the role of hyperglycemia and diabetes duration on this association [10]. Khan et al. reported the strongest correlation between these two entities in the literature, finding an odd ratio of 2.74 for diabetes [11]. On the other hand, as already mentioned in ''Introduction'', other studies did not confirm this association [12,13,18]; it has been suggested that the reasons for these conflicting results may be differences in sample sizes, grades of WMH, diabetes severity and diabetes duration across the various study populations [19]. Another potential factor leading to discordant results could be related to heterogeneity in the assessment of WML. Several segmentation techniques have been used in order to assess the severity of LA [20]. In our study, a neuroradiologist with 12 years of experience evaluated the presence and number of WML lesions on FLAIR sequences; then, WML volume was automatically calculated using a semi-automated segmentation technique. This semi-automated system was assumed to provide a reproducible assessment of WML.

Due to these previously described issues, most authors agree that the strength of the association between diabetes and LA is unclear and that further investigations are certainly needed [3,4]. The importance of this association is nevertheless clear since the impact that LA has on everyday life is well recognized. WML has been demonstrated to be correlated with onset of urinary urgencies [21], stroke incidence [22,23], clinical outcome after ischemic stroke [24], abnormal neurological examination [25]. Moreover, the extent of LA has been proven to independently predict 90-day recurrent stroke risk after ischemic stroke, suggesting how LA extension may be used for risk stratification in ischemic stroke [8].

Our study suggested again a mild, but statistically significant, correlation between diabetes and WML, both in terms of number and volume of lesions ($P < 0.0001$); the strength of our work is that the two investigated sub-populations did not show any significant difference regarding all the other non-modifiable and modifiable risk factors (age, sex, smoking habits, hypertension, CAD, dyslipidemia); this let us to focus only on the influence of diabetes in LA development. On the other hand, the first limitation of our study is the relatively small cohort; in addition, since our patients were all scheduled for CEA and because of the lack of comparison with healthy subjects, our results regard a sub-population affected by arterial disease and cannot be simply extended to the whole population. The patients from this study are not representative of a general population; therefore, the results should be further confirmed by other studies before being considered for general purposes. Another limitation was related to the concept of the duration of diabetes; some authors demonstrated a correlation between diabetes duration and WLM [13], but we did not evaluate this kind of correlation in our patients' series.

In conclusion, our results support the evidence that diabetes is significantly associated with LA, probably playing a role in the small vessel disease considered as the main cause of the most common MRI findings of WML disease. Further larger studies are needed to confirm this observation and to determine whether the same trend really exists also in healthy asymptomatic patients; after that, the scientific challenge could be the identification of potential therapeutic targets and the creation of dedicated screening protocols for WML disease in diabetic patients other than the simple measurement of LA total burden.

Keypoints

- Diabetic patients had larger WML lesions compared with non-diabetic patients.
- Diabetic patients had more WML lesions compared with non-diabetic patients.
- Multivariate statistical analysis demonstrated that only diabetes was statistically associated with WML.

Disclosure of interest

The authors declare that they have no competing interest.

Authors had full control of all the data and information presented in this manuscript.

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