SHORT COMMUNICATION

Cardiovascular risk factors and the association between grey matter volume and white matter lesions

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DOI: 10.33963/KP.a2022.0290

Received:
August 31, 2022

Accepted:
November 18, 2022

Early publication date:
December 14, 2022

INTRODUCTION

Spheres of abnormal myelination in the brain, referred to as white matter lesions (WMLs) or leukoaraiosis [1], are frequently detected by magnetic resonance imaging (MRI) of the central nervous system. The appearance and distribution of WMLs may be caused by numerous vascular and non-vascular factors [2] but, generally speaking, any damage leading to a change in the composition of myelin fibers may be observed as WMLs on MRI. These formations are common in elderly individuals, ranging from discrete to more confluent and extensive volume lesions. Additionally, a recent investigation showed that these age-related findings are not benign [3, 4], and therefore WMLs are regarded as predictors of future risk of stroke, dementia, and frailty, as well as reduction of grey matter volume (GMV). It was also reported that GMV decline is associated with the risk of dementia [5]. The current study investigated whether there is a correlation between WMLs and GMV and whether various cardiovascular (CV) risk factors, particularly those that can be pharmacologically modified (e.g. hypertension, diabetes), influence this association.

METHODS

The study population involved 251 high-risk patients subjected to brain MRI performed during a neurological assessment for transient ischemic attack (TIA) and low-risk subjects without obvious cerebral insult (e.g., headache, episodic vertigo). It represented consecutive subjects selected from an existing database. The patients also comprised those without or with risk factors (such as hypertension and/or diabetes) and/or TIA. Diabetes and hypertension were defined by standard criteria and diagnosed before the current hospitalization. TIA was described as a sudden onset of a focal neurologic symptom and/or sign lasting less than 24 hours and analyzed before the recent hospitalization. Laboratory parameters including creatinine concentration and serum glucose were assessed using standard methods in the central hospital laboratory.

We used a 1.5T MRI scanner (Avanto Siemens Medical System, Erlangen, Germany) with a 12-channel head RF coil to obtain brain images. Our study protocol consisted of axial, sagittal T1-weighted, T2-weighted, FLAIR and DWI sequences, three-dimensional T1-weighted images (Magnetisation Prepared Rapid Acquisition Gradient Echo [MPRAGE]; TR/TE/IR, 2 400 ms/3.61 ms/1000 ms; section thickness, 1.2 mm). The MPRAGE sequence was used to calculate brain volume. WMLs were defined as hyperintensities on T2 weighted and FLAIR (Fluid-attenuated inversion recovery) sequences on MRI and detected automatically by the FREESurfer algorithm. Total grey matter volume includes both surface-based volume calculations and voxel counts performed automatically by the FREESurfer algorithm. FreeSurfer software (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging) was used to analyze brain structures.

Statistical analysis

Continuous data were reported as the mean (standard deviation [SD]). Normal distribution was assessed with the D'Agostino-Pearson omnibus normality test. The differences between means were assessed using Student's t-tests. The Pearson correlation coefficient was calculated, and linear regression was

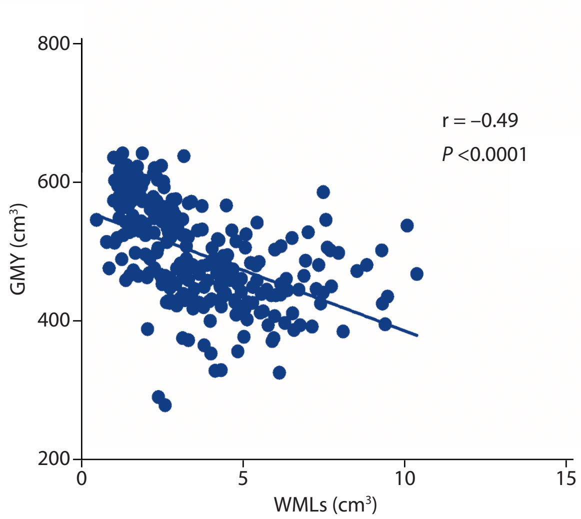

Figure 1. Association between grey matter volume (GMV) and white matter lesions (WMLs)

performed. The association of grey matter volume with other clinical variables was examined with the use of multivariable regression. The significant *P*-level was set at <0.05. Relevant analyses were conducted using GraphPad Prism (Version 5, GraphPad Software, San Diego, CA, US), MedCalc® Statistical Software version 20.110 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022), and JMP Pro 16.1 (SAS Institute Inc., Cary, NC, US).

RESULTS AND DISCUSSION

The clinical characteristics of the study subjects are presented in Supplementary material, *Table S1*. The mean age of the studied population was 66 years whilst males made up 55% of the respondents and females 45%. The subjects demonstrated a combination of CV risk factors, such as transient ischemic attacks (TIA; 56%), hypertension (48%), and diabetes (19%).

There was a strong negative correlation between GMV and WMLs (r = –0.49, *P* <0.0001, Figure 1). Moreover, subjects without CV risk factors had significantly more GMV than patients with CV risk factors (575 [31] cm^3 vs. 461 [55] cm^3, *P* <0.001, Supplementary material, *Figure S1A*). Similar results were noted when WMLs were compared between both groups (2.1 [1.3] cm^3 vs. 4.2 [1.9] cm^3; *P* <0.001, Supplementary material, *Figure S1B*). A similar difference was also observed when GMV and WMLs were indexed for body mass index (BMI, data not shown).

Multiple linear regression revealed that GMV was associated with age, sex, systolic BP, history of hypertension, diabetes, TIA, and WMLs volume (Supplementary material, *Table S1*), with these factors explaining 61% of the variance in GMV observed in the current study.

In this study, WMLs were negatively associated with GMV. Moreover, WMLs increased when GMV decreased in subjects with a spectrum of CV risk factors. Furthermore, GMV was significantly influenced by sex, age, systolic blood pressure, history of hypertension, diabetes, TIA as well as WMLs.

WMLs are frequently observed on brain MRI, particularly in older subjects. Once regarded as benign, they are currently thought to result in cognitive decline, stroke, or death. The brains of subjects with WMLs also demonstrate other changes, including lacunar infarcts and signs of grey matter atrophy. Raji et al. [6] evaluated 740 cognitively normal controls using MRI, showing that WMLs were inversely correlated with GMV whilst the most significant volume loss was seen in the frontal cortex. Cardiovascular risk factors are associated with cognitive impairment and dementia. The Multi-Ethnic Study of Atherosclerosis evaluated the association of brain volumes and white matter injury with ethnicity and CV risk factors (CVRF) [7]. After adjustment for various risk factors and socioeconomic status, there was no difference in white matter injury by ethnicity. However, the results supported the important effect of modifiable risk factors, such as smoking or hypertension, on WMLs. Evidence for the association between various CV risk factors and GMV was conflicting due to adaptable characteristics of some of these markers, e.g., hypertension, diabetes control, smoking status, and weight. Felissati et al. [8] observed 134 cognitively unimpaired older adults (>65 years), noting that lower insulin levels and BMI, as well as a higher rate of physical activity, were associated with larger GMV. The present study found no correlation between BMI and GMV (data not shown), and the inclusion of BMI in the regression model did not influence the overall fit of regression (data not shown). Despite several research studies, there remains limited evidence for the association between CV risk factors, WMLs, and the brain macrostructure. Cox et al. [9] observed that higher number of risk factors were associated with poorer "brain health" across both grey and white matter macro and microstructures. The present study showed that the subjects with one or more CV risk factors (hypertension, diabetes, past TIA) had significantly lower GMV and a larger number of WMLs. These subjects were also older and had higher systolic blood pressure. The adjusted regression model explained that 61% of the variance in GMV was caused by older age, male sex, higher blood pressure, presence of hypertension, TIA, and a more significant number of WMLs.

Study limitations: this study analyzed results obtained from a combination of subjects with and without obvious brain insult, so the conclusion should be limited to this population. Moreover, this study assessed the correlation between variables — this analysis does not determine causation.

In conclusion, our findings underscore that vascular risk factors and WMLs are associated with lower GMV in mixed populations of subjects with and without blatant brain insult. Moreover, WMLs are not only associated with vascular brain injury; they may also be involved in the pathophysiological process of brain atrophy. It is tempting to speculate that modifying risk factors (diet, hypertension, exercise program, etc.) may improve the macrostructure of the brain and delay the development of grey matter atrophy. Therefore, it seems that patients with WMLs and vascular risk factors should be advised on lifestyle changes and aggressive control of comorbidities [10].

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

Conflict of interest: None declared.

Funding: None.

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