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Distribution and frequency of cerebral microhemorrhages in cerebral small vessel disease

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ABSTRACT

Aim: To evaluate the distribution and frequency of microhemorrhages (MHs) in cerebral small vessel disease (CSVD), multiple lacunar stroke and control groups and their association with factors implicated in etiology such as hypertension (HT), diabetes mellitus (DM) and antiplatelet drug use.

Methods: Patients were divided into CSVD, multiple lacunar infarction (MLI) and control groups based on white matter hyperintensity (WMH), presence of lacunes, and patient clinical information. The presence and frequency of MHs were compared in terms of comorbidities such as accompanying HT, DM and antiplatelet use.

Results: The presence of MHs in the CSVD group was significantly higher than in the other groups (p<0.001). The number of MHs in the thalamus, basal ganglia and cortical-subcortical areas were significantly higher in the CSVD group than in the other groups.

Conclusions: One of the most important points that stands out in this study is that microhemorrhage was seen in 78% in the CSVD group, 38% in the MLI group and 20% in the control group, although the total number did not exceed three. The results of our study suggest that T2* gradient echo (GE) and susceptibility weighted (SW) imaging should be performed before thrombolytic therapy in stroke patients with or without CSVD.

Key words: Small vessel disease, gradient echo, microhemorrhages, acute stroke.

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Introduction

Cerebral small vessel disease (CSVD) is the involvement of cerebral small arteries, arterioles, capillaries and veins by various mechanisms and pathologies [1]. Among the imaging modalities, magnetic resonance imaging (MRI) provides the best visualization of the findings of CSVD. It is possible to detect CSVD through secondary changes in imaging modalities such as new small subcortical infarcts, lacunar infarcts, white matter hyperintensity (WMH), enlarged perivascular space and the presence of microhemorrhages (MH) [2]. Clinically, ischemic outcomes are mostly expected when it comes to CSVD, and it should be kept in mind that the clinical outcome may be micro or macrohemorrhages depending on the pathogenesis of the underlying CSVD [1, 2]. It has been reported that the acute and short-term prognosis of strokes in CSVD is better compared to other strokes [3]. However, the long-term

results are not better in terms of mortality and loss of function [4]. Thrombolytic therapy with tissue plasminogen activators (tPA) is an accepted treatment modality in stroke patients [5] but increases the risk of symptomatic intracerebral hemorrhage in patients with leukoaraiosis [6].

Microbleeds or microhemorrhages, can be visualized as hypointense foci on T2*-weighted gradient echo (GE) and susceptibility-weighted (SW) images [7]. The diameter of the MHs is usually between 2-5 mm, sometimes reaching up to 10 mm [2]. Localization of MHs may be informative about the underlying etiological cause. Parietal lobe localized MHs with cortical-subcortical localization are associated with apolipoprotein E-4 (ApoE4) carriage [8]; MHs with cortical-subcortical localization are more commonly associated with cerebral amyloid angiopathy, while MHs located in deep cerebral areas are associated with hypertension or atherosclerotic microangiopathy. Hypertension may also cause mixed involvement in deep and subcortical areas [9]. The frequency of MHs increases with age and ApoE4 carriage [10]. MHs have also been associated with antiplatelet drug use [11].

There is an increased risk of stroke in the presence of MHs [8]. Significant problems arise in the use of antiaggregants, anticoagulants and recombinant tissue plasminogen activator (tPA) in the treatment of acute ischemic stroke [12]. In patients with anticoagulant use, the risk of intracranial hemorrhage increases 5.5-fold in the presence of 5 or more cerebral MHs [13].

In addition to CSVD, the risk of multiple lacunar infarction is increased in the presence of hypertension (HT) or diabetes mellitus (DM) [14]. The risk of arteriolosclerosis, which is the etiology of small vessel disease, increases with HT, DM and age [1]. The aim of our study was to evaluate the distribution-frequency of MHs in CSVD, multiple lacunar infarction (MLI) and control groups and their association with etiologic factors such as hypertension (HT), diabetes mellitus (DM) and antiplatelet (AP) use.

Materials and methods

In this study, we retrospectively reviewed 600 brain MRI scans performed between February 2018 and February 2020 in patients aged ≥50 years. Ethics committee approval 2023/289 was obtained from the ethics committee of Local Instution. Patients with primary-metastatic brain tumors, history of head and neck region cranial radiotherapy, parenchymal macrohemorrhage and large areas of sequelae encephalomalacia, history of head trauma, and motion artifact in T2*-weighted gradient echo sequence were excluded from the study. A total of 184 patients were included in the study. Patients were evaluated for the presence of WMH, enlarged perivascular distance and MH, which are the MRI findings of CSVD. These patients were divided into groups based on WMH, presence of lacunes, and patient clinical information. Patients with diffuse WMH and variable number of lacunar infarcts were defined as the CSVD group, patients with multiple lacunar infarcts and mild to moderate WMH were defined as the MLI group, and patients with 1 or 2 lacunar infarcts without a history of stroke who were imaged for reasons such as headache and vertigo were defined as the control group.

The presence, localization and number of MHs were evaluated in these groups. Cerebellum, brainstem, thalamus, basal ganglia were classified as deep; MHs located in the cortical-subcortical area, white matter were classified as superficial and those in both areas were classified as deep&superficial [9] (Figure 1a, 1b, 1c). The difference in the distribution of MHs between the groups and their association

with the factors implicated in the etiology were evaluated.

MHs, lacunar infarcts, and the consensus proposed by Wardlaw et al. [2] according to the grouping of enlarged PVSs by Kwee et al. [15]. Those with diffusely enlarged PVS at the level of basal ganglia, especially in the corpus striatum, were evaluated as etat crible [16, 17].

Lacunar infarcts are 3-15 mm in diameter, oval or round shaped cavities with a central fluid signal on fluid-attenuated inversion recovery (FLAIR) sequence and a hyperintense rim at the periphery, similar to CSF [2], (Figure 1d).
Enlarged perivascular spaces, another imaging finding in CSVD, are seen in all pulse sequences in the same way as cerebrospinal fluid (CSF). Those in the sublenticular area adjacent to the lenticulostriate arteries were classified as type 1, those around the medullary perforating arteries extending from the cortex to the white matter at the convexity level were classified as type 2, and those around the collicular-accessory collicular arteries in the lower midbrain at the pontomesencephalic junction were classified as type 3 [15].

The Fazekas scale finds extensive application in both clinical practice and research for visually grading white matter hyperintensities (WMH) in magnetic resonance imaging (MRI) data [18]. WMHs are rated as Fazekas 1, 2 and 3 according to the Fazekas classification [19].

The presence of HT, DM and history of antiplatelet use were evaluated in all patient groups.

***Statistical analysis**:* Statistical analyses were performed with SPSS software (SPSS 22 for Mac, IBM Co., Chicago, IL, USA). The normality of distribution of the data was evaluated by Shapiro-Wilk test. Kruskal-Wallis test was used to compare distribution of numerical non-parametric variables. Rows by column Pearson Chi-square test and Fisher Freeman Halton test were used to analyze categorical data. A p-value less than 0.05 is considered statistically significant.

Results

In this study, 64 patients (22 females, 42 males) were included in the CSVD group, 55 patients (26 females, 29 males) in the MLI group and 61 patients (33 females, 28 males) in the control group. There was no statistical difference between the groups in terms of gender (p=0.08). The median (min-max) age values of the groups were 76 (54-85), 74 (57-86) and 70 (52-87) in CSVD, MLI and control groups, respectively, with no statistical difference between the groups (p=0.1). There was no statistical difference between the groups in terms of the presence of HT and DM and antiplatelet use (p=0.05-0.74-0.08, respectively) (Table 1).

Table 1. Demographic data and number-percentages of risk group diseases in cerebral small vessel disease (CSVD), multiple lacunar infarction (MLI) and control groups.

Parameters	CSVD (n=64)	MLI (n=55)	Control group (n=61)	*p*-value
Age (Median) (Min-Max)	76 (54-85)	74 (57-86)	70 (52-87)	0.1[a]
Gender (Female/Male)	22/42	26/29	33/28	0.08[b]
Hypertension	47 (%73)	39 (%71)	33 (%54)	0.05[b]
Diabetes Mellitus	20 (%31)	19 (%35)	17 (%28)	0.74[b]
Antiplatelet drug use	34 (%53)	35 (%64)	26 (%43)	0.77[b]

[a]: Kruskal Wallis Test, [b]: R by C Pearson Chi-square test.

Table 2. Presence and distribution of microhemorrhages in cerebral small vessel disease (CSVD), multiple lacunar infarction (MLI) and control groups.

Parameters	CSVD (n=64)	MLI (n=55)	Control group (n=61)	*p*-value
Presence of microhemorrhages	50 (%78)	21 (%38)	12 (%20)	**<0.001[a]**
Deep settlement	13 (%20)	5 (%9)	3 (%5)	**<0.001[b]**
Superficial settlement	7 (%11)	3 (%6)	6 (%10)	
Deep+superficial settlement	30 (%47)	13 (%24)	3 (%5)	
Non-microhemorrhage	14 (%22)	34 (%62)	49 (%80)	

[a] *:Fisher Freeman Halton test* [b]*: R by C Pearson Chi-square.*

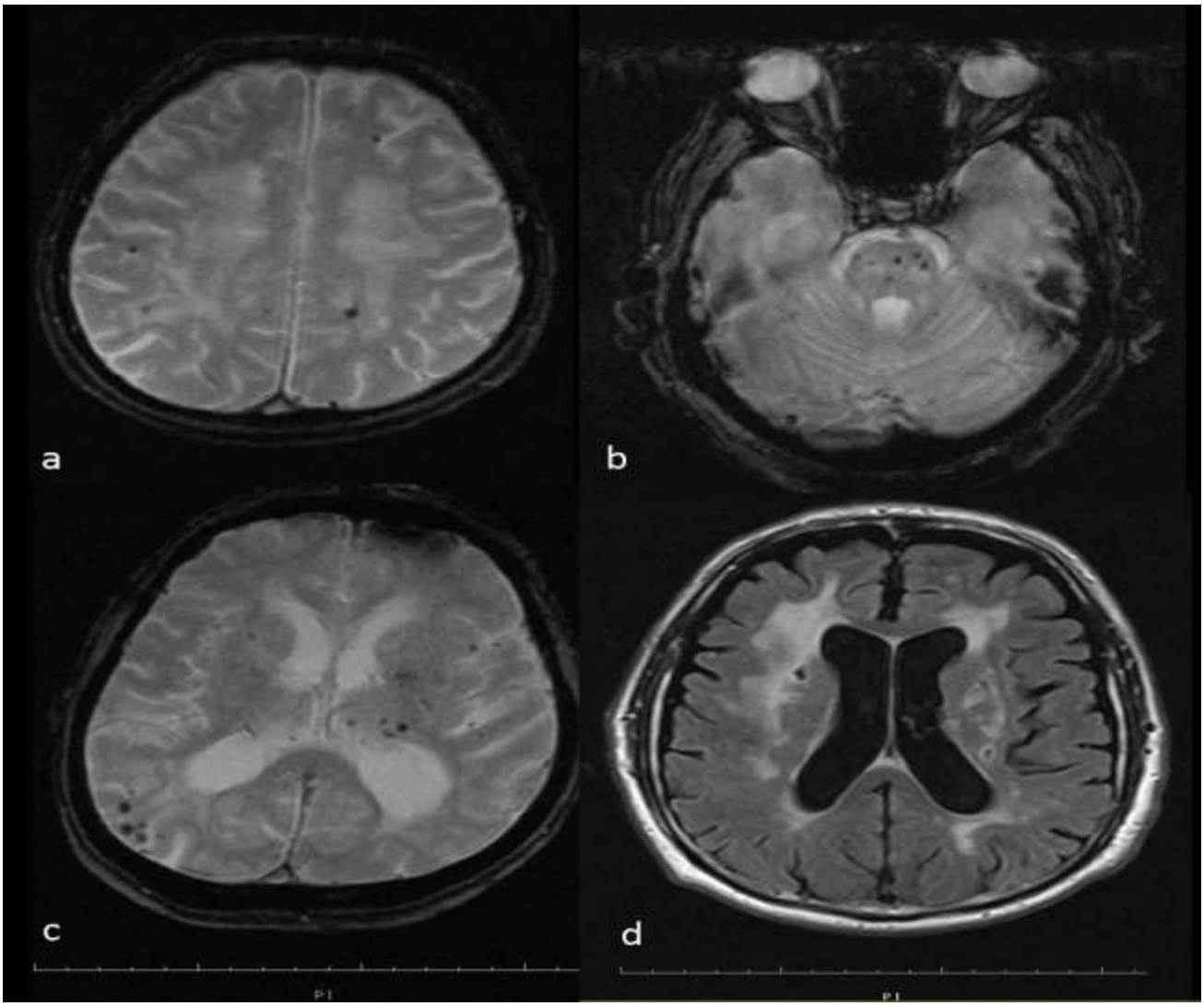

Figure 1. Superficial, deep, deep&superficial microbleeds were observed as hypointense foci on axial T2* gradient eco images (**a, b,c**, respectively), **d:** In the axial FLAIR image, lacunar infarcts are seen in the bilateral lentiform nuclei with hypointense central and hyperintense rim on the periphery are observed.

There was a statistically significant difference between the groups in the evaluation of the presence of microbleeding. Especially this rate was significantly higher in the CSVD group (p<0.001). Deep and deep&superficial MHs are significantly more common in CSVD compared to other groups (p<0.001) (Table 2) (Figure 1a, 1b, 1c). There was a statistically significant difference between the groups in the cerebellum in the evaluation of the number of microhemorrhages, especially in the CSVD group, more microhemorrhages were observed than in the control group similar to MLI (p=0.002). There was no statistically significant difference between the groups in the evaluation of microhemorrhages in the brain stem and white matter, respectively (p=0.44, p=0.07).

In the evaluation of microhemorrhages, they were observed in the thalamus, basal ganglia and cortical-subcortical localization, more in the CSVD group and there was a statistically significant difference between the groups (p<0.001, p=0.002, p=0.04 respectively) (Table 3).

When perivascular spaces were analyzed, it was observed that the type 1 perivascular space was significantly higher in the CSVD group compared to the other groups (p<0.001).

Discussion

In this study, the presence of MHs in all areas and the number in the thalamus, basal ganglia and cortical-subcortical areas were significantly

Table 3. Number of microhemorrhages by localization in cerebral small vessel disease (CSVD), multiple lacunar infarction (MLI) and control groups.

Number of microhemorrhages		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**>15**	***p*-value**
Cerebellum	**CSVD**	42	14	6	1	0	1												**0.002***
	MLI	47	7	1	0	0	0												
	Control group	59	2	0	0	0	0												
Brain stem	**CSVD**	53	5	2	0	1	1	1	1										0.44*
	MLI	48	3	2	1	0	1	0	0										
	Control group	60	1	0	0	0	0	0	0										
Thalamus	**CSVD**	31	7	6	3	6	2	4	1	1	0	0	0	0	3				**<0.001***
	MLI	41	5	4	1	1	2	0	0	0	0	0	0	1	0				
	Control group	59	2	0	0	0	0	0	0	0	0	0	0	0	0				
Basal ganglia	**CSVD**	37	5	7	4	7	1	1	1	0	0	0	0	1	0				**0.002***
	MLI	41	8	3	1	1	0	1	0	0	0	0	0	0	0				
	Control group	59	1	1	0	0	0	0	0	0	0	0	0	0	0				
White matter	**CSVD**	52	9	2	1														0.07*
	MLI	52	3	0	0														
	Control group	59	2	0	0														
Cortical-subcortical	**CSVD**	30	11	7	3	1	2	1	0	4	1					1	0	3	**0.04***
	MLI	39	7	3	1	1	1	0	1	0	0					0	1	1	
	Control group	55	5	1	0	0	0	0	0	0	0					0	0	0	

** Fisher Freeman Halton test were used to analyze categorical data.*

higher in the CSVD group than in the MLI and control groups. The presence and number of MHs were significantly higher in the CSVD group compared to the MLI and control groups. There was no significant difference between the groups in terms of HT, DM and antiplatelet use which may be involved in the etiology of MHs. However, the presence and number of deep-seated, deep&superficial localized MHs were significantly higher in the CSVD group as seen in HT [9].

In the literature, there are publications indicating that the number and deep-superficial occurrence of MHs may be helpful in predicting the severity and risks of the underlying predominant pathology [20]. Although the blood pressure regulation status of our patients is not known, this suggests that blood pressure control is actually more important than HT history in the development of CSVD. This is supported by publications showing that blood pressure regulation is important in terms of the development of microbleeds and intracerebral hemorrhage [21].

One of the most important points that stands out in this study is that microhemorrhage was seen in 78% in the CSVD group, 38% in the MLI group and 20% in the control group, although the total number did not exceed three. T2* GE and SW imaging should be performed before thrombolytic therapy in stroke patients with or without CSVD. There are studies supporting this in the literature [22]. In the presence of deep-seated MHs, HT control is an important factor in the development of spontaneous intracranial hemorrhage.

In the literature, there are publications showing a direct correlation between CSVD and the risk of ischemic stroke or spontaneous intracranial hemorrhage, and this has also been shown to be directly related to prognosis [23]. A postmortem histopathologic study has also shown an association between MHs and spontaneous intracranial hemorrhage [24].
Bleeding risk associated with leukoaraiosis and lacunar infarcts in stroke treatment may also be secondary to microbleeds [6, 25]. Leukoaraiosis is a term mostly used in computed tomography (CT) and CT was used in these studies, and since MHs were not detected, the bleeding risk may have been associated with lacunar infarction and leukoariosis, which are findings of CSVD.

There are also publications in the literature showing an increased risk of cerebral hemorrhage or hemorrhagic transformation after thrombolytic therapy in patients with old microbleeds, and therefore, detection of microbleeds becomes important [22, 26, 27]. However, there are studies showing that the risk of intracranial hemorrhage is less than the probability of exceeding the benefits of thrombolytic therapy, and it is recommended to make a patient-based decision based on the benefit-risk ratio [28]. In stroke patients, if MRI cannot be performed due to reasons such as the importance of time, the protocol of the stroke center, etc., the patient's recent brain MRI examinations, if any, should also be evaluated for the presence of old microbleeds.

Microhemorrhages can be confused with calcification, normal vascular structures on cross section, iron deposits due to other causes and hemorrhagic micrometastases such as malignant melanoma, diffuse axonal injury due to head trauma [2]. Microhemorrhages are also radiologically indistinguishable from microdissections, microaneurysms, microcalcifications and arteriolar pseudocalcifications [7]. One of the limitations of this study is that it was performed with 2D T2* GE sequence. This may lead an increase in false positive cases. Pre-post mortem radiology-histopathology concordance studies found that at least half of MHs could not be demonstrated by

imaging methods [7, 20]. The best agreement between radiology and histopathology is with 7 T MRI devices, but these devices are not yet used in daily routine practice [7, 29]. Demonstration of MHs is enhanced by magnetic field strength, 3D sequences and postprocessing and can be differentiated from calcifications with phase images [7].

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