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ORIGINAL RESEARCH

Absence of susceptibility vessel sign with cancer-associated hypercoagulability-related stroke

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ABSTRACT

BACKGROUND AND PURPOSE: Susceptibility vessel sign (SVS), a hypointense signal on MR T2-weighted gradient-recalled echo images, is associated with erythrocyte-predominant thrombi, which are often present in cardioembolism (CE). In contrast, cancer-associated hypercoagulability (CAH)-related stroke, which is presumably caused by fibrin-predominant thrombi, is associated with the absence of SVS. We hypothesized that the prevalence of SVS may be of help in distinguishing CAH-related stroke from CE. This study attempted to validate this hypothesis and investigated the usefulness of SVS in differentiating CAH-related stroke from CE.

MATERIALS AND METHODS: We retrospectively studied both CAH-related stroke patients (CAH group) and CE patients (CE group), who had major cerebral artery occlusion on MR angiography that was performed within 6 hours of stroke onset. All patients visited our department from 2015 to 2021. CAH-related stroke was defined as 1) complication of active cancer, 2) pre-treatment D-dimer value >3 μg/mL, 3) multiple vascular territories infarctions, and 4) lack of any other specifically identified causes of stroke. We compared SVS positivity rates within each group. Multivariable logistic regression analysis was used to assess the association between the absence of SVS and CAH-related stroke.

RESULTS: Of 691 patients with CAH-related stroke or CE, major cerebral artery occlusion was observed in 10 patients in the CAH group and 198 patients in the CE group. The absence of SVS was identified in 55 of 208 patients and was significantly more frequent in the CAH versus the CE group (90% versus 24%, $p < 0.05$). For predicting CAH-related stroke, absence of SVS demonstrated a sensitivity of 90% (95% confidence interval [95%CI] 59-99), specificity of 78% (95%CI 71-83), positive predictive value of 18 (95%CI 10-31), negative predictive value of 99% (95%CI 96-99), and a likelihood ratio of 4.06. Multivariable logistic regression analysis revealed that the absent of SVS was independently associated with CAH-related stroke (odds ratio 43, 95% [CI] 6.8-863; $p < 0.01$).

CONCLUSIONS: The absence of SVS was more frequent in CAH-related stroke versus that found for CE. These findings could potentially be helpful for clinical management and differentiating between CE and CAH-related stroke.

ABBREVIATIONS: CAH, cancer-associated hypercoagulability; CE, cardioembolism; SVS, susceptibility vessel sign; GRE, gradient recalled echo.

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SUMMARY SECTION

PREVIOUS LITERATURE: Susceptibility vessel sign (SVS) has been shown to be associated with the component of the thrombi. The SVS positivity rate is high in cardioembolism (CE)due to the erythrocyte-predominant thrombi, while in atherothrombotic brain infarction, the rate is low due to the fibrin-predominant thrombi. Moreover, it has been reported that a higher proportion of stroke patients with active cancer exhibit the absence of SVS as compared to those without. However, there are no reports focusing on cancer associated hypercoagulability (CAH)-related stroke in patients with active cancer.

KEY FINDINGS: The absence of SVS was more frequent in CAH-related stroke compared to that for CE and it was independently associated with the CAH-related stroke. When differentiating between these two types of strokes, the absence of SVS indicates there is a higher likelihood of CAH-related stroke.

KNOWLEDGE ADVANCEMENT: The difference in thrombopathology may attribute to the difference in the frequency of SVS in CE and CAH-related stroke. The absence of SVS is valuable in distinguishing between CE and CAH-related stroke in embolic stroke of undetermined source and may serve as a guide in making clinical decisions in these cases.

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INTRODUCTION

Introduction should be placed here. Please write a brief introduction to the paper that outlines the Background/Purpose in further detail. Cancer patients face an elevated risk of ischemic stroke, with cancer-associated hypercoagulability (CAH) being the primary mechanism contributing to this elevated risk.(1–3) CAH-related stroke is characterized by the presence of high D-dimer levels and multiple vascular territories infarctions.(4–6) In some cases, patients with CAH-related stroke experience major cerebral artery occlusion and exhibit similar MRI findings to those observed for cardioembolism (CE).(7–9)

CAH-related stroke and CE both require antithrombotic therapy in order to prevent recurrence, but the choice of the agent is specific for each mechanism. Typically, direct oral anticoagulants or warfarin are used in CE, while subcutaneous heparin is preferred in CAH-related stroke.(2,10) Thus, it is crucial to be able to distinguish between CAH-related stroke and CE in order to prevent stroke recurrences.

Furthermore, CE and CAH-related stroke contribute to the etiology of embolic stroke of undetermined source. Given the differing clinical management strategies for suspected CE and CAH-related stroke in the etiology of embolic stroke of undetermined source, the differentiation between the two conditions is crucial in determining the clinical management strategies.

Susceptibility vessel sign (SVS), which is detected as a hypointense signal on the T2* gradient-recalled echo images (GRE), is associated with a high proportion of deoxyhemoglobin within the thrombus. Erythrocyte-rich thrombi, which are typically seen in CE, are likely to show SVS, while fibrin-predominant thrombi, which are typically found in atherothrombotic brain infarction, are less likely to show this. It has been previously reported that SVS can be useful in helping to distinguish atherothrombotic brain infarction from CE.(11–15) Although the thrombus found in CAH-related stroke has also been reported to be fibrin predominant,(8,16,17) SVS has yet to be fully investigated in CAH-related stroke patients, and thus, the diagnostic role of SVS in CAH-related stroke remains unclear. The purpose of this study was to investigate the usefulness of SVS in distinguishing CAH-related stroke from CE.

MATERIALS AND METHODS

Design

This study was a retrospective observational study of patients who were diagnosed with ischemic stroke at a tertiary stroke center (Kyoto Second Red Cross Hospital, Kyoto, Japan). The need to obtain informed consent for participation was waived due to the retrospective design and the minimal risk to patients.

Study patients

Of the 2476 acute ischemic stroke patients that were admitted to the Kyoto Second Red Cross Hospital within 7 days after stroke onset between April 2015 and March 2021, we enrolled both the CAH-related stroke patients and CE patients with major cerebral artery occlusion. Acute ischemic stroke was defined as any new neurological symptom with acute ischemic lesions confirmed by diffusion weighted imaging. CAH-related stroke was defined using the following criteria: 1) complication of active cancer, 2) pre-treatment D-dimer value >3 μg/mL, 3) multiple vascular territories infarctions, and 4) lack of any other specifically identified causes of stroke.(18) CE was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.(19) Major cerebral artery occlusion was defined as carotid T occlusion, M1-middle cerebral artery occlusion, or M2-middle cerebral artery occlusion. We excluded patients who did not undergo an MRI scan within 6 hours of onset. Active cancer was defined as a diagnosis or treatment for any cancer within 6 months prior to ischemic stroke onset, or known recurrent cancer or metastatic disease. Patients with focal non-melanoma skin cancer and those treated with prophylactic hormone therapy for prior breast cancer were classified as not having active cancer. (20)

Measurements

Using previous medical records, we collected data regarding age, sex, cardioembolic source, type of cancer, time from onset to MRI, pre-treatment D-dimer levels, diffusion weighted image findings, and vascular imaging. The three-territory sign was defined as the presence of lesions in the three vascular territories of the bilateral anterior and posterior circulation.(21)

Outcomes

The primary outcome was the positivity of SVS. SVS was defined as a hypointense signal on the T2*GRE at a corresponding symptomatic occlusive vessel, for which the signal exceeded the estimated diameter of the artery (Figure 1).(22) SVS was assessed by two independent stroke-specialized neurologists (D.F. and J.F.). When the judgment of the two neurologists was inconsistent, a decision was made by discussion without the consideration of any information other than the T2*GRE.

MRI protocol

Two MRI models were used: Philips Ingenia 1.5T and Siemens Magnetom Avanto 1.5T. The T2*GRE sequence was examined using the following parameters: repetition time/echo time = 459/18 ms, flip angle = 20 degrees, slice thickness = 6 mm, slice gap = 0.6 mm, acquisition time 80 sec, matrix = 208 × 209, and field of view = 220 mm.

Statistical analysis

Fisher's exact test and the Mann-Whitney U test were used, as appropriate, to compare the clinical characteristics between the CAH and the CE groups. The κ coefficient was used to determine the interobserver agreement for SVS on T2*GRE. Multivariable logistic regression analysis was used to investigate the association between the absence of SVS and the CAH-related stroke. The level of significance was considered to be 0.05 in all tests. All statistical analyses were performed using GraphPad Prism version 9.4.1 (GraphPad Software LLC, CA, USA).

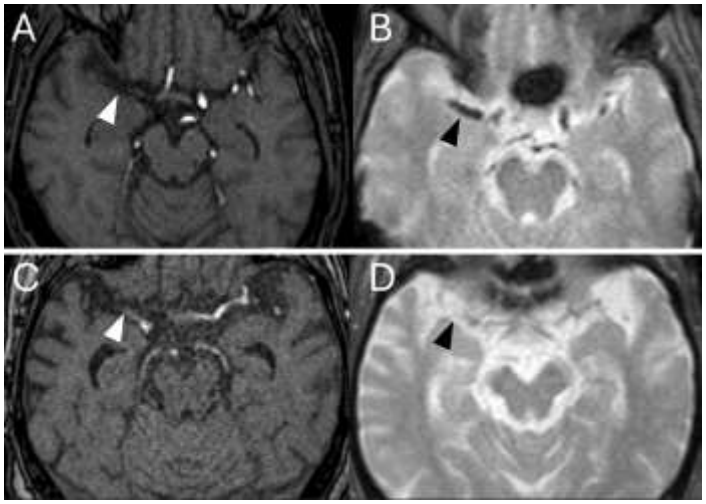

FIG 1. Assessment of the susceptibility vessel sign. (A,B) Complete occlusion of the right MCAon arterial TOF (A), with the presence of SVS on the T2*GRE (B). (C,D)) Complete occlusion of the right MCA on arterial TOF (C), with the absence of SVS on the T2*GRE (D). Arrowhead indicates the part of the vessel occlusion on the TOF and T2*GRE. SVS susceptibility vessel sign, MCA middle cerebral artery, TOF time-of-flight angiography, GRE gradient recalled echo images.

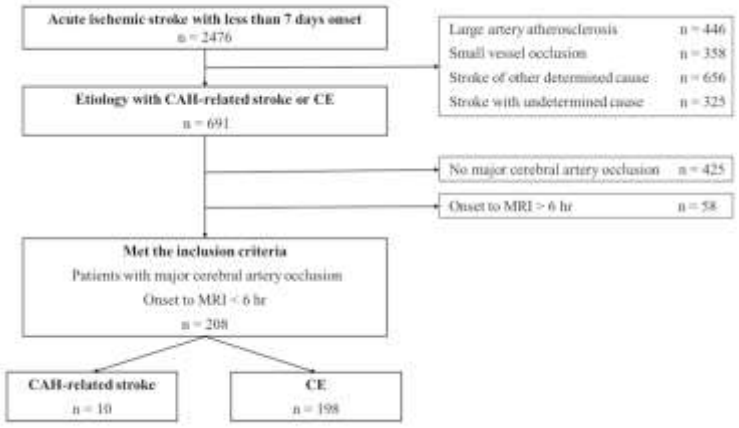

FIG 2. Study flow chart for the inclusion of subjects. MRI magnetic resonance imaging, CAH cancer-associated hypercoagulability, CE cardioembolism.

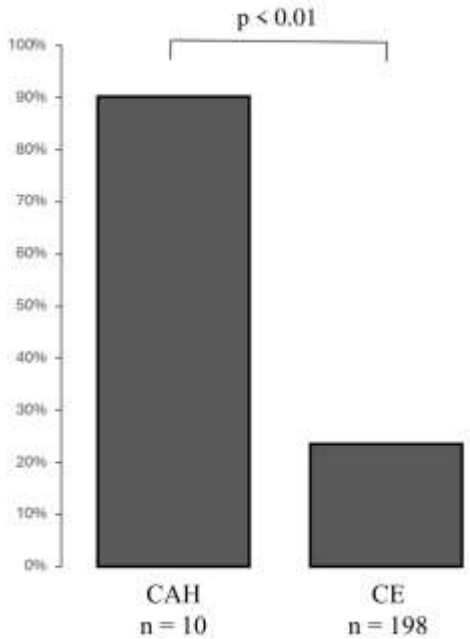

FIG 3. Proportion of the absence of SVS in each group. SVS susceptibility vessel sign, CAH cancer-associated hypercoagulability, CE cardioembolism.

RESULTS

A flow diagram of the patient selection is presented in Figure 2. The final cohort consisted of 208 acute ischemic stroke patients with major cerebral artery occlusion, which included 10 in the CAH and 198 in the CE groups. The most prevalent cancer types were lung cancer (3 cases) and pancreatic cancer (3 cases). For CE, embolic sources included atrial fibrillation in 186 cases, symptomatic congestive heart failure in 5 cases, paradoxical embolism in 4 cases, and recent myocardial infarction, calcified aortic stenosis, and mechanical valve in 1 case each. Table 1 presents the baseline characteristics.

SVS was absent in 55 patients (26%), with 9 cases in the CAH and 46 cases in the CE groups. The absence of SVS was more frequent in the CAH versus the CE group ($p < 0.01$) (Figure 3). The absence of SVS was observed in 22% for ICA, 11% for M1, and 29% for M2. The κ coefficients for interobserver agreement of SVS by the 2 examiners were 0.87 and 0.98, while it was 0.92 for the interobserver agreement of SVS. The disagreement rate between the two examiners was 9%.

To assess the performance of the absence of SVS with regard to differentiating the CAH-related stroke from CE, multivariable logistic regression analysis was used to identify the association factor for the CAH-related stroke. Results revealed that the absence of SVS was independently associated with the CAH-related stroke (odds ratio 43, 95% confidence interval [95%CI] 6.8-860; $p < 0.01$) (Table 2). The absence of SVS demonstrated a sensitivity of 90% (95%CI 59-99), specificity of 78% (95%CI 71-83), positive predictive value of 18% (95%CI 10-31), negative predictive value of 99% (95%CI 96-99), and likelihood ratio of 4.06 for predicting CAH-related stroke. The presence of SVS demonstrated a sensitivity of 78% (95%CI 71-83), specificity of 90% (95%CI 59-99), positive predictive value of 99% (95%CI 96-99), negative predictive value of 18% (95%CI 9-30), and a likelihood ratio of 7.78 for predicting CE.

DISCUSSION

The present results showed that the absence of SVS was more frequent in CAH-related stroke compared to that for CE. When differentiating between these two types of strokes, the absence of SVS indicates there is a higher likelihood of CAH-related stroke.

The high proportion of CAH-related stroke with the absence of SVS may be attributed to the fibrin-predominant thrombi that were present. SVS has been shown to be associated with the presence of deoxyhemoglobin, methemoglobin, and hemosiderin within the erythrocytes of the thrombi.(11,23) In fact, the SVS positivity rate is high (56-89%) in CE due to the erythrocyte-predominant thrombi, while in atherothrombotic brain infarction, the rate is low (19-53%) due to the fibrin-predominant thrombi.(12,14,24,25) Similarly, it has been reported that a higher proportion of stroke patients with active cancer exhibit the absence of SVS as compared to those without.(20) This might be attributable to the fact that fibrin-predominant thrombi are more frequently observed in stroke patients with active cancer.(26) Fibrin-predominant thrombi are more frequently observed in CAH-related stroke, which is the main subtype of stroke in patients with active cancer, as compared to that found in CE or atherothrombotic brain infarction.(27) In the present study, we selected CAH-related stroke study subjects from any of the stroke subtypes in patients with active cancer. Thus, the proportion of CAH-related stroke with the absence of SVS was markedly high at 90%.

In recent years, mechanical thrombectomy has provided insights into the characteristics of retrieved thrombus. Case reports have shown the presence of fibrin-predominant thrombus pathology in CAH-related stroke.(8,16,17) Thrombus formation in CAH-related stroke involves multiple mechanisms leading to hypercoagulability. First, when the vascular endothelium is damaged by high flow or inflammatory cytokines produced by cancer cells, platelets will then adhere to the exposed area of the endothelium. Subsequently, platelets aggregate through an interaction with the activated von Willebrand factor. Cancer cells cause hypercoagulability through mechanisms such as activating the coagulation cascade with tissue factor, directly activating prothrombin with mucin, and directly activating factor X with cysteine protease. The hypercoagulability leads to the formation of a fibrin-predominant thrombus under high flow arterial conditions, which then leads to less entrapment of the red blood cells.(28)

The findings of the present study have the potential for clinical significance in being able to distinguish between CE and CAH-related stroke within the context of embolic stroke of undetermined source. Embolic stroke of undetermined source represents a subset of cryptogenic strokes, and accounts for approximately 25% of all ischemic strokes. The causes of embolic stroke of undetermined source include subclinical paroxysmal atrial fibrillation, aortogenic embolism, paradoxical embolism, and cancer-associated stroke.(29) While these etiologies all have similar features such as embolic stroke, microvascular invasions, and elevated D-dimer levels, the aortogenic embolism and paradoxical embolism can be diagnosed through additional modalities, such as contrast-enhanced angiography or transesophageal echocardiography. As in the present study, although the CE is characterized by the present of an elderly age as compared to that found for CAH-related stroke, the differentiation between CE and CAH-related stroke remains challenging. When trying to identify the specific causes, such as subclinical paroxysmal atrial fibrillation, and underlying malignancy remains elusive in these cases. In such cases, the absence of SVS may serve as a guide in making clinical decisions. In summary, SVS serves as a guide for clinical management strategies. These strategies may involve repeated Holter ECG monitoring or the use of an implantable loop recorder. Conversely, if SVS is absent, vigilant monitoring will be necessary in order to detect these malignancies. This includes further investigations and early stage re-examination of the cancer using CT scans or other diagnostic modalities.

However, we need to acknowledge that there were several limitations for the present study. First, this was a single-center, retrospective study, and thus, a selection bias may exist. Also, given the small number of study patients and low incidence of CAH-related stroke, the sample size was significantly unbalanced, which reduced the power of statistical analysis in the present study. Thus, further studies with larger numbers of cases and multicenter studies are needed. Second, there were some disagreements with the SVS assessment between the two examiners. However, the interobserver agreement was high enough to be considered satisfactory. Third, the slice thickness and slice gap of the T2*GRE at our center were 6mm/0.6mm, which is rather thick for assessing cerebral vessels, and thus, this may have affected the SVS evaluation. Moreover, since SVS evaluation did not use susceptibility-weighted imaging, which is more sensitive than T2*GRE, it is possible that the absence of SVS may have been overestimated. Fourth, since the appearance and quality of T2*GRE can vary, the present findings may not be fully generalizable. Finally, the thrombus pathology was not assessed. Nevertheless, since in actual clinical practice the thrombopathology is not always confirmed, the results of the current study may be clinically valuable with regard to future

diagnostic and management strategies.

Table 1: Baseline characteristics.

	CAH-related stroke n = 10	CE n = 198	p value
Age	73 (67-77)	82 (74-89)	<0.05
Female	7 (70)	100 (54)	0.53
Onset to MRI (min)	180 (80-285)	128 (70-180)	0.18
Major cerebral artery occlusion			
ICA	1 (10)	20 (11)	0.99
M1	2 (20)	71 (38)	0.32
M2	7 (70)	94 (51)	0.33
Three territory sign	9 (90)	5 (3)	<0.01
D-dimer (μg/mL)	27 (23-32)	2 (1-4)	<0.01

Values are n (%), or medians (interquartile range). ICA internal carotid artery, CAH cancer-associated hypercoagulability, CE cardioembolism.

Table 2: Multivariable logistic regression analysis for the absence of SVS.

	Odds ratio	95% CI	p value
Female	0.8	0.3-1.6	0.50
Age > 60	1	0.9-1.0	0.38
M2 occlusion	2.5	1.2-5.3	0.03
CAH-related stroke	43	6.8-860	<0.01

SVS susceptibility vessel sign, CAH cancer-associated hypercoagulability, CI confidence interval.

CONCLUSIONS

The absence of SVS was more frequent in CAH-related stroke as compared to than that found in CE. Thus, the absence of SVS might be an important factor for the clinical management and the ability to differentiate between CE and CAH-related stroke.

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