의학석사 학위 논문

FLAIR vascular hyperintensities predict early ischemic recurrence in transient ischemic attack

초기 병변이 없는 일과성 허혈 발작 환자에서 FLAIR 영상의 혈관 고강도 신호가 추적 영상 병변에 미치는 영향

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이 논문을 의학 석사학위논문으로 제출함

2018 년 4 월

서울대학교 대학원

의학과 중개의학 전공

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남기웅의 석사학위 논문을 인준함

2018 년 7 월

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Abstract

FLAIR vascular hyperintensities predict early ischemic recurrence in transient ischemic attack

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Though lesion negative transient ischemic attack (TIA) patients accounted for considerable amounts in clinical fields, their diagnoses are interrupted with many mimic diseases (e.g., seizure, migraine, hypoglycemia, psychotic disease). To assess more objective diagnosis of true ischemic origin TIA patients, we evaluated the relationship between FLAIR vascular hyperintensity (FVH) and early ischemic lesion recurrence [FU-DWI (+)] in lesion negative transient ischemic attack (TIA) patients.

We recruited consecutive lesion negative TIA patients within 24 hours of symptom onset, who underwent follow-up MRI during the acute period. FVH was defined as a focal or serpentine high signal intensity on FLAIR images. Furthermore, to compare clinical outcomes between the FU-DWI (+) and FU-DWI (-) groups, we assessed 1-year recurrent ischemic stroke or TIA.

Among 392 lesion negative TIA patients, 82 patients had FU-DWI (+) on the follow-up MRI. In the multivariate analysis, FVH remained an independent predictor of FU-DWI (+) [adjusted OR (aOR) = 4.77, 95% confidence interval (CI) 2.45-9.29, $P < 0.001$]. The time to initial MRI (aOR = 0.49, 95% CI = 0.33-0.70, $P < 0.001$) and intracranial atherosclerosis (aOR = 2.07, 95% CI = 1.10-3.92, $P = 0.025$) were also associated with FU-DWI (+), independent of FVH. In clinical outcomes, the FU-DWI (+) group showed more frequent 1-year recurrent ischemic stroke events than the FU-DWI (-) group (10.7% versus 3.1%, respectively, $P = 0.007$).

FVH is associated with FU-DWI (+) in lesion negative TIA patients. As FU-DWI (+) commonly occurs during the acute period and has a subsequent worse outcome after discharge, additional radiological or clinical markers for it are necessary.

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Keywords: Transient ischemic attack, Fluid-attenuated inversion recovery,

Prognosis, Ischemic stroke, Recurrence, Cerebral perfusion, Collaterals

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Introduction

Fluid attenuated inversion recovery vascular hyperintensity (FVH) is commonly identified via magnetic resonance imaging (MRI), when the proximal large artery is occluded or severe stenosis is present.(1) It indicates slow anterograde or retrograde leptomeningeal collaterals, presenting an absence of flow-void phenomenon a result of sluggish blood flow.(2-4) With the development of thrombolysis therapy, early detection of perfusion defects and evaluation of collateral flows have been focused. Thus, FVH, which is an non-invasive parameter of both perfusion defects and collaterals, has been evaluated in many studies on ischemic stroke.(5, 6) On the other hand, in transient ischemic attack (TIA) patients, although FVH is also commonly present,(7-9) its clinical meanings have not been well addressed.

Early ischemic lesion recurrence based on MRI is important in ischemic stroke and TIA patients, showing subsequent poor prognosis despite more frequent asymptomatic recurrences than overt clinical recurrence.(10-12) However, in the aspect of TIA, these studies were only designed to include combined TIA and minor ischemic stroke patients.(13, 14) Thus, the prevalence and clinical meanings of early ischemic lesion recurrence in isolated TIA patients have remained elusive. Furthermore, they suggested the identification of multiple lesions via diffusion weighted imaging (DWI), and a large artery atherosclerosis stroke mechanism as predictors of early ischemic lesion recurrence.(13) However, these predictors were

not adjustable in many TIA patients who had no lesions via DWI.

The importance of DWI lesions in TIA patients has been well established in many previous findings.(15-18) On the other hand, patients who had no lesion on initial MRI (lesion negative TIA) have been relatively ignored, although they account for substantial portions of TIA and many of them result from ischemic events. As initial DWI images could not provide clues for them, the exact TIA mechanisms, natural courses, and ideal treatment plans are difficult to predict. Thus, additional radiological markers of ischemic events are necessary in this group. In this study, we aimed to evaluate the relationship between FVH and early ischemic lesion recurrence with its clinical meanings in lesion negative TIA patients.

Material and Methods

Patients and population

As part of a consecutive stroke registry in two large centers in Korea (Seoul National University Hospital and Seoul National University Bundang Hospital) between January 2010 and December 2015, patients who were diagnosed with TIA within 24 hours of symptom onset were selected (n = 867). TIA was defined as a sudden neurologic disability that lasted < 24 hours as a result of a cerebral thromboembolic event.(7) In our centers, all patients who were clinically diagnosed

as TIA were principally admitted and underwent stroke etiology evaluation, including brain MRI, magnetic resonance angiography (MRA), echocardiography, and laboratory examinations, within 24 hours of admission. Furthermore, we conducted follow-up brain MRI in most cases during the early acute period of TIA to evaluate the mechanisms of TIA or early ischemic lesion recurrence if there was no contraindication.

To conduct this study, patients who had no lesion on initial MRI (lesion negative TIA) were extracted (n = 442). We subsequently excluded participants who met the following criteria: younger than 18 years (n = 6), lack of initial and follow-up MRI data (n = 37), or presence of premorbid severe functional disability with a modified Rankin Scale score (mRS) > 2 (n = 7). Finally, 392 patients were included in the analyses (Figure 1). This study was approved by the Institutional Review Board at Seoul National University Hospital (IRB No. H-1707-027-867).

Clinical assessment

We collected baseline demographic, clinical, and cardiovascular risk factors, including age, sex, hypertension, diabetes, hyperlipidemia, atrial fibrillation, current smoking, previous history of stroke, and initial systolic/diastolic blood pressure. Laboratory data regarding the glucose profile, lipid profile, levels of C-reactive

protein (CRP), and white blood cell counts were also assessed. The $ABCD^2$ scores were reviewed using medical records and were rated by well-trained neurologists at the time of admission.(19) All clinical and laboratory factors were fully assessed in all participants.

We evaluated the clinical outcomes after discharge from the initial TIA events to determine the clinical meanings of early ischemic lesion recurrence using the 1-year recurrence of TIA or ischemic stroke. We defined recurrent ischemic stroke only when a new clinical event was accompanied with a new lesion on brain MRI, being spatially distinct from the index lesion.(20) The secondary endpoint was defined as the last time to follow-up or the first time to the recurred event.

Radiological assessment

All participants in the study underwent brain MRI and MRA within 24 hours of admission and follow-up images during early acute periods using a 3.0-T MR scanner (Achieva 3.0T; Philips, Eindohoven, the Netherlands). The basic thickness of a slice was 5.0 mm in the axial plane, and the detailed acquisitions of the MRI were as follows; DWI [repetition time (TR) / echo time (TE) = 6300/80 or 4800/66], T1-weighted images (TR/TE = 500/10 or 300/10), T2-weighted images (TR/TE = 5100/90 or 4800/100), fluid-attenuated inversion recovery images (FLAIR) (TR/TE

= 10,000/90 or 11,000/140), T2-gradient echo images (TR/TE = 57/20 or 28/20), and three-dimensional time-of-flight MRA images (TR/TE = 20/7, slice thickness = 1.2 mm). FVH was defined as a focal, tubular, or serpentine high-signal intensity along the typical course of a blood vessel on FLAIR images (Figure 2).(7) We rated only the ipsilateral FVH, which was correlated with the localization of initial clinical symptoms. The topography of FVH was also rated in four areas (anterior cerebral artery, anterior half of middle cerebral artery, posterior half of middle cerebral artery, posterior cerebral artery) of each hemisphere, according to previous study. (21) Intracranial atherosclerosis (ICAS) and extracranial atherosclerosis (ECAS) were defined as an occlusion or more than 50% stenosis of each vessel on flight MRA images.(22, 23)

We subsequently dichotomized the cohort into FU-DWI (+) and FU-DWI (-) groups by the presence of a DWI lesion on the follow-up MRI, without considering the presence of symptomatic recurrence. To determine the pathophysiologic mechanisms of these early ischemic lesion recurrences, we classified the FU-DWI (+) lesions into 6 categories as follows; 1) Only-cortical, 2) Cortical-subcortical, 3) Single small subcortical (≤ 20 mm), 4) Large perforator, 5) Border zone, and 6) Multiple territory. Detailed descriptions and examples of each category are presented in Figure 3. The presence of FVH, ICAS, and ECAS and the classification of FU-DWI (+) lesions were rated by two neurologists only with information regarding the initial clinical symptoms; the mean inter-rater reliability coefficient

was $P = 0.863$ (FVH: 0.866, ICAS: 0.919 ECAS: 0.891 DWI (+) lesion classification: 0.776). Disagreements were resolved by the discussion with a third rater.

Statistical analysis

All variables with a normal distribution were presented as the mean ± standard deviation, whereas other variables were presented as median + interquartile ranges. Univariate analyses for the evaluation between the FU-DWI (+) and FU-DWI (-) groups were conducted using Student's *t*-test or the Mann-Whitney *U*-test for continuous variables and chi-squared test or Fisher's exact test for the categorical variables. Continuous variables with skewed data were transformed into a log scale. All variables with $P < 0.05$ and an $ABCD^2$ score were introduced into the multivariate logistic regression analysis. As FVH is closely related to ICAS ($P < 0.001$, Pearson correlation efficient), we created a new variable of [FVH x ICAS] by multiplying two categorical variables and conducted an additional multivariate analysis to reduce their interaction effects as a sensitivity analysis.

To compare the clinical outcomes between the FU-DWI (+) and FU-DWI (-) groups, we used the Kaplan-Meier analysis using FU-DWI (+) and 1-year recurrent TIA or ischemic stroke. Variables with $P < 0.05$ were considered significant, and all

statistical analyses were performed using SPSS version 23.0 (IBM, SPSS, Chicago, IL, USA).

Results

We collected a total of 392 lesion-negative TIA patients. Eighty-two (21%) patients had early ischemic lesion recurrences on the follow-up MRI [FU-DWI (+)], in which the median volume of the lesions was 0.37 [0.16-1.08] mL. Among them, 12 (15%) had symptomatic FU-DWI (+) events. The median time to the initial MRI was 3 hours compared with 2.5 days for the follow-up MRI. Sixty-four (16%) patients showed ipsilateral FVH on the initial MRI.

The baseline characteristics of the FU-DWI (+) and FU-DWI (-) groups are presented in Table 1. The FU-DWI (+) group tended to have a shorter time to the initial MRI from symptom onset, higher levels of CRP, more frequent male sex, hyperlipidemia, FVH, and ICAS. Although there was no significant difference in the $ABCD^2$ scores, the items regarding a longer duration of symptoms and clinical symptoms with unilateral weakness were more frequent in the FU-DWI (+) group (Table 2). In the multivariate analysis, FVH remained an independent predictor of FU-DWI (+) [adjusted OR (aOR) = 4.77, 95% confidence interval (CI) 2.45-9.29, $P < 0.001$, Table 3]. Additionally, the time to initial MRI (aOR = 0.49, 95% CI 0.33-

0.70, $P < 0.001$) and ICAS (aOR = 2.07, 95% CI = 1.10-3.92, $P = 0.025$) were also associated with FU-DWI (+), independent of FVH. These results continued after additional adjusting with [FVH x ICAS], which reduced the interaction between FVH and ICAS (Table 4). FVH also had significance when we conducted additional analysis, excluding patients who had symptomatic ICAS (Table 5).

To understand the individual meanings of FVH and ICAS on early ischemic lesion recurrence, we divided the cohort into four groups [FVH (-) ICAS (-), FVH (-) ICAS (+), FVH (+) ICAS (-), and FVH (+) ICAS (+)]. In the FVH (+) ICAS (+) group, FU-DWI (+) most frequently occurred (64%), whereas the FVH (-) ICAS (-) group showed the least frequency (13%) ($P < 0.001$, Chi-squared test) (Figure 4). The FVH (+) ICAS (-) group showed more frequent FU-DWI (+) than the FVH (-) ICAS (+) group (42% versus 23%, $P = 0.049$, Figure 4), and there was an incremental tendency among the 4 groups ($P < 0.001$, linear-by-linear association analysis).

We subsequently analyzed 82 FU-DWI (+) lesions to determine the pathophysiologic mechanisms of early ischemic lesion recurrence. Only-cortical (32%) and single small subcortical patterns (32%) were most frequently identified in the cohort (Figure 5). Between the four groups with and without FVH and ICAS, the FVH (+) ICAS (+) group showed a frequent cortical-subcortical pattern ($P < 0.001$) and less frequent single small subcortical pattern ($P = 0.035$), in a dose-

response manner ($P < 0.001$ and $P = 0.007$, respectively), which was favorable for large-artery disease (Figure 6). The FVH (+) ICAS (-) group showed the most frequent only-cortical pattern; however, it was not statistically significant (Figure 7).

To determine the clinical meanings of early ischemic lesion recurrence, we compared the 1-year recurrent ischemic stroke or TIA events between the FU-DWI (+) and FU-DWI (-) groups. The median follow-up duration of the cohort was 944 days, and 73% of the cases had complete a 1-year follow-up. The FU-DWI (+) group showed more frequent recurrent ischemic stroke events than the FU-DWI (-) group (10.7% versus 3.1%, respectively, $P = 0.007$), whereas the recurrent TIA events were not different (4.1% versus 1.9%, respectively, $P = 0.290$) (Figure 8). This difference remained significant when we adjusted age and sex as confounders (Cox regression analysis; Adjusted hazard ratio = 3.70, 95% CI = 1.36-10.08, $P = 0.011$). Interestingly, patients who had initial ipsilateral FVH also showed poorer prognosis in 1-year recurrent ischemic stroke events (10.5% versus 3.6%, $P = 0.025$), but not in 1-year TIA recurrence (3.4% versus 2.1%, $P = 0.526$).

Discussion

In this study, we found that ipsilateral FVH is associated with early ischemic lesion recurrence [FU-DWI (+)] in lesion negative TIA patients. Furthermore, the FU-

DWI (+) group had a poorer prognosis in the aspect of 1-year recurrent stroke than did the FU-DWI (-) group.

We determined that FVH is closely correlated with FU-DWI (+). FVH is known to be caused by large artery disease.(1) Thus, the close relationship between FVH and FU-DWI (+) may be the result of the effects of ICAS or ECAS. As indicated in this study, FVH was closely associated with ICAS, and the FVH (+) ICAS (+) group showed the most frequent FU-DWI (+), presenting a synergistic effect. Additionally, the FVH (+) ICAS (+) group most frequently showed cortical-subcortical patterns, which likely result from large artery disease, mostly in the territory of ICAS. Thus, ICAS would be one of main connectors in the pathophysiology between FVH and FU-DWI (+).

However, FVH may also be used as a predictor of FU-DWI (+) independent of ICAS. The FVH (+) ICAS (-) group presented frequent FU-DWI (+), even more than the FVH (-) ICAS (+) group. Furthermore, FVH remained significant after adjusting [FVH x ICAS], which was created to reduce the interaction between FVH and ICAS. And these results continued when we conducted additional analysis, excluding patients who had symptomatic ICAS. In addition to these statistical findings, the FVH (+) ICAS (-) group showed predominant only-cortical patterns, which were considered as a marker of distal embolization from the large artery. In contrast, the FVH (-) ICAS (-) and FVH (-) ICAS (+) groups showed mostly single

small subcortical patterns, preferring lacunar stroke mechanisms, and the FVH (+) ICAS (+) group presented frequent cortical-subcortical patterns, which indicate large artery disease. Based on both the statistical and radiological results, we suggest that FVH may also be used as an independent marker of early ischemic lesion recurrence, with a different mechanism from ICAS.

The rate of 1-year recurrent ischemic stroke in the entire cohort was 4.8%, and it was relatively less than the known TIA prognosis.(24, 25) Although the frequencies of recurrence may be underestimated using our strict definition of recurrent ischemic stroke, the lesion negative TIA group appeared to have a favorable prognosis. Additionally, if patients had no lesion on the follow-up DWI images [FU-DWI (-)], they had only a 3.1% chance of recurrence, which was less than half the rate of the FU-DWI (+) group. Because we determined the subsequent prognosis would depend on the presence of early ischemic lesion recurrence, which was the same as in other stroke groups,(10-12) early follow-up brain MRI would be needed also in the lesion negative TIA group.

Our study has several caveats. First, this study was designed as a two-center single-ethnic based study. Although we had a relatively large sample size of this group, selection bias may be possible, and generalization to a non-Asian population, which exhibits less frequent ICAS, should be cautious. Second, we only included patients who had follow-up brain MRI, which may also result in the possibility of

bias. However, we could not collect all lesion negative TIA cases, we conducted an extensive imaging evaluation using broad acquisitions of brain MRI and MRA during both the initial and acute follow-up periods. We also classified follow-up DWI lesion patterns with consideration of its mechanisms. Thus, this study had meanings of not only novel radiological marker identification in lesion negative TIA patients but also the determination of its clinical meanings and clues regarding the pathophysiologic mechanisms. Last, since we included lesion negative TIA patients based on initial clinical impression, some of them (13%) finally diagnosed as TIA mimic diseases (seizure, migraine, functional disorder, and others). However, since FVH remained significant when we conducted multivariate analysis without these 50 patients (aOR = 4.70, 95% CI = 2.38-9.29, $P < 0.001$), our implications would not be changed.

In conclusion, FVH is associated with early ischemic lesion recurrence in patients with lesion negative TIA independent of ICAS. As the FU-DWI (+) group accounted for considerable proportions during the early acute period and showed a worse outcome after discharge, conducting follow-up MRI in early acute period would be needed. Additionally, the recent clinical trial showed intensive antiplatelet therapy in TIA patients reduced subsequent stroke risk without hemorrhage.(26) Our findings may suggest clues for further studies about making selection criteria for intensive antiplatelet treatments in this group.

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Tables

Table 1. Baseline characteristics of FU-DWI (+) and FU-DWI (-) groups

	FU-DWI (-) (n = 310)	**FU-DWI (+) (n = 82)**	***P*-Value**
Age, year [IQR]	64 [53-73]	64 [53-72]	0.653
Time to initial MRI, h [IQR] [a]	3.5 [2.0-5.5]	2.0 [1.0-3.5]	< 0.001
Sex, Male %	160 (52)	56 (68)	0.007
Hypertension, %	176 (57)	44 (54)	0.613
Diabetes, %	86 (28)	20 (24)	0.543
Hyperlipidemia, %	89 (29)	33 (40)	0.045
Atrial fibrillation, %	23 (7)	11 (13)	0.086
Current smoking, %	43 (14)	17 (21)	0.125
History of stroke, %	63 (20)	14 (17)	0.510
Initial SBP, mmHg	152 [136-171]	152 [139-175]	0.370
Initial DBP, mmHg	84 [74-94]	85 [78-95]	0.331
White blood cell, x $10^3/\mu L$	6.90 [5.70-8.40]	6.70 [5.72-8.40]	0.822
hs-CRP, mg/dL [a]	0.08 [0.03-0.30]	0.03 [0.03-0.15]	0.021
FLAIR vascular hyperintensity, %	31 (10)	33 (40)	< 0.001
Internal cerebral atherosclerosis, %	63 (20)	34 (41)	< 0.001
External cerebral atherosclerosis, %	23 (7)	9 (11)	0.296
$ABCD^2$ score [IQR]	4 [3-5]	4 [4-5]	0.100

hs-CRP = high-sensitive C-reactive protein

[a] These variables were introduced as a log scale

Table 2. Differences regarding detailed items of the ABCD^2 score between FU-DWI (+) and FU-DWI (-) groups

	FU-DWI (-) (n =310)	FU-DWI (+) (n =82)	*P*-Value
Age			0.689
≥ 60 years	189 (61)	48 (59)	
< 60 years	121 (39)	34 (41)	
Blood pressure			0.436
High group	217 (70)	61 (74)	
Low group	93 (30)	21 (26)	
Clinical symptoms			0.009
Unilateral weakness	141 (45)	52 (63)	
Speech disturbance	81 (26)	18 (22)	
Others symptoms	88 (28)	12 (15)	
Durations of symptoms			0.019
≥ 60 minutes	141 (45)	29 (35)	
10~59 minutes	103 (33)	41 (50)	
< 10 minutes	66 (21)	12 (15)	
Diabetes			0.543
Yes	86 (28)	20 (24)	
No	224 (72)	62 (76)	

Table 3. Multivariate analysis of potential predictors of FU-DWI (+)

	Crude OR	*P*-Value	Adjusted OR	*P*-Value
Sex, Male, %	2.02 [1.21-3.38]	0.008	1.82 [0.99-3.32]	0.052
Time to initial MRI*, h	0.50 [0.36-0.69]	< 0.001	0.48 [0.33-0.70]	< 0.001
Hyperlipidemia, %	1.67 [1.01-2.77]	0.046	1.35 [0.74-0.49]	0.329
hs-CRP [a], mg/dL	0.86 [0.71-1.05]	0.135	0.84 [0.68-1.03]	0.096
FVH, %	6.06 [3.41-10.79]	< 0.001	4.77 [2.45-9.29]	< 0.001
ICAS, %	2.78 [1.65-4.67]	< 0.001	2.07 [1.10-3.92]	0.025
$ABCD^2$ score	1.13 [0.96-1.33]	0.157	1.20 [0.98-1.46]	0.079

hs-CRP = high-sensitive C-reactive protein, FVH = FLAIR vascular hyperintensity, ICAS = Intracranial atherosclerosis

[a] These variables were introduced as a log scale

Table 4. Multivariate analysis of potential predictors of FU-DWI (+) group, adjusting for interaction effects.

	Crude OR	*P*-Value	Adjusted OR	*P*-Value
Sex	2.02 [1.21-3.38]	0.008	1.82 [0.99-3.31]	0.052
Time to initial MRI*	0.50 [0.36-0.69]	< 0.001	0.48 [0.33-0.70]	< 0.001
Hyperlipidemia	1.67 [1.01-2.77]	0.046	1.35 [0.74-2.49]	0.330
hs-CRP*	0.86 [0.71-1.05]	0.135	0.84 [0.68-1.03]	0.099
FVH	6.06 [3.41-10.79]	< 0.001	4.87 [2.11-11.26]	< 0.001
ICAS	2.78 [1.65-4.67]	< 0.001	0.94 [0.24-3.69]	0.052
FVH x ICAS	8.44 [3.72-19.13]	< 0.001	0.94 [0.24-3.69]	0.932
$ABCD^2$ score	1.13 [0.96-1.33]	0.157	1.20 [0.98-1.46]	0.079

hs-CRP = high-sensitive C-reactive protein, FVH = FLAIR vascular hyperintensity, ICAS = Intracranial atherosclerosis

* These variables were introduced as a log scale

Table 5. Multivariate analysis of potential predictors of FU-DWI (+) group, excluding participants who had symptomatic ICAS.

	Crude OR	*P*-Value	Adjusted OR	*P*-Value
Sex	2.14 [1.14-4.01]	0.017	1.76 [0.85-3.63]	0.125
Time to initial MRI [a]	0.43 [0.29-0.66]	< 0.001	0.34 [0.20-0.55]	< 0.001
Hyperlipidemia	1.76 [0.96-3.20]	0.066	1.50 [0.72-3.10]	0.276
hs-CRP [a]	0.84 [0.67-1.05]	0.131	0.91 [0.72-1.16]	0.466
FVH	5.64 [2.76-11.54]	< 0.001	7.10 [3.04-16.61]	< 0.001
ICAS	1.72 [0.73-4.05]	0.218	1.72 [0.61-4.83]	0.301
$ABCD^2$ score	1.33 [1.08-1.63]	0.007	1.52 [1.17-1.96]	0.002

hs-CRP = high-sensitive C-reactive protein, FVH = FLAIR vascular hyperintensity, ICAS = Intracranial atherosclerosis

[a]These variables were introduced as a log scale

Figures

Figure 1. Patient flow-chart of the cohort

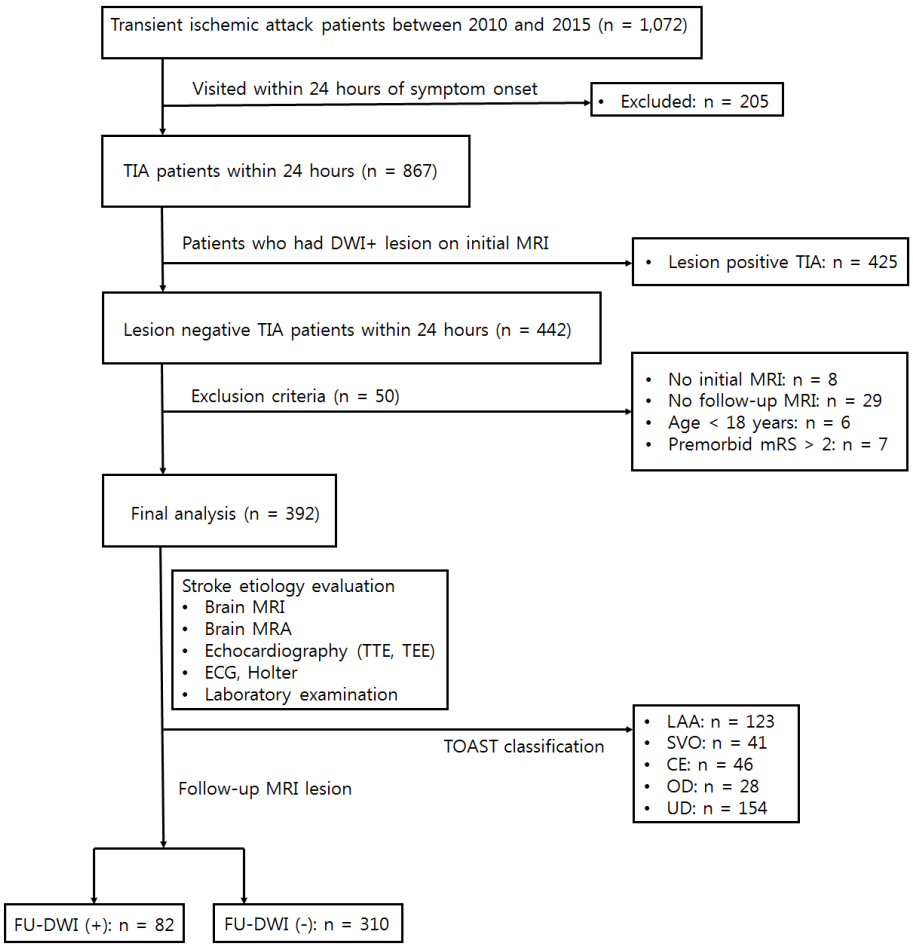


Figure 2. Representative cases of FVH

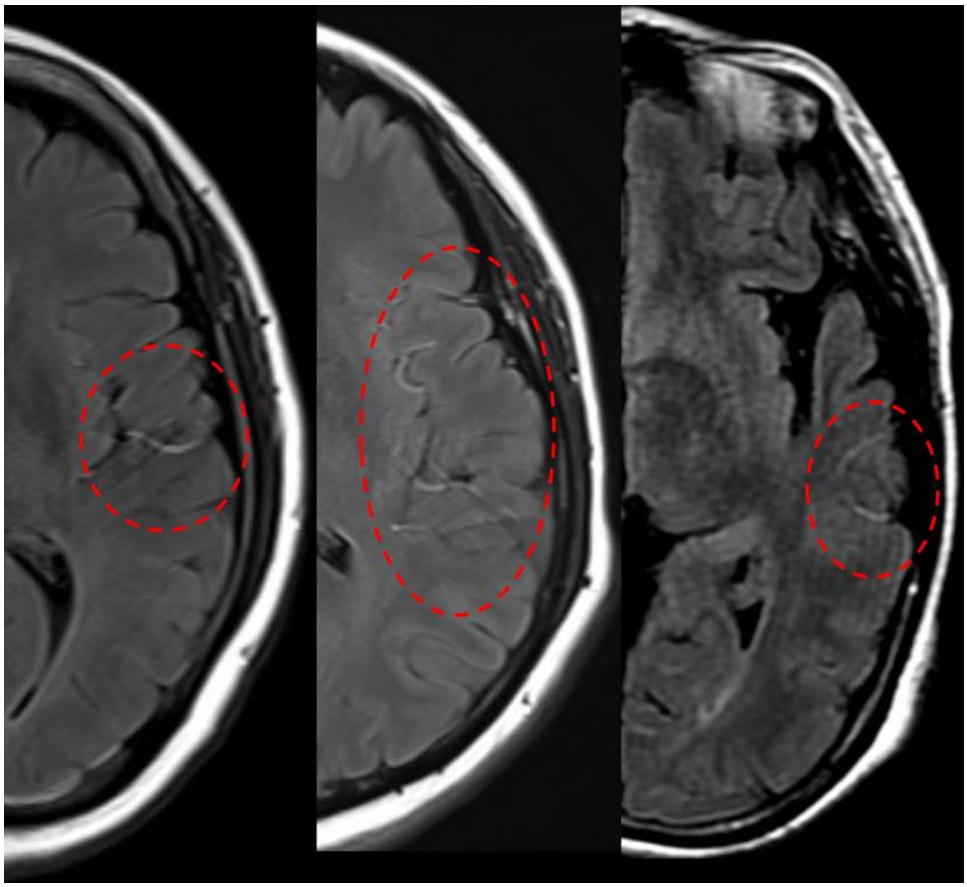
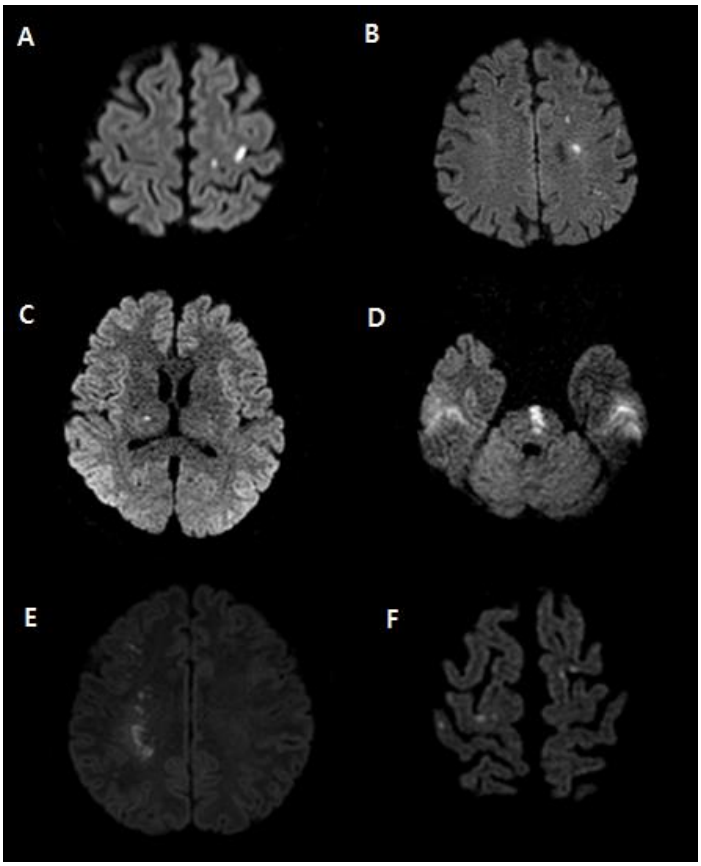


Figure 3. Definitions and examples of the patterns of FU-DWI (+) lesions



A. Only-cortical: lesions in only cortical surface without subcortical lesions in a single vascular territory

B. Cortical-subcortical: lesions in both cortical and subcortical areas in a single vascular territory

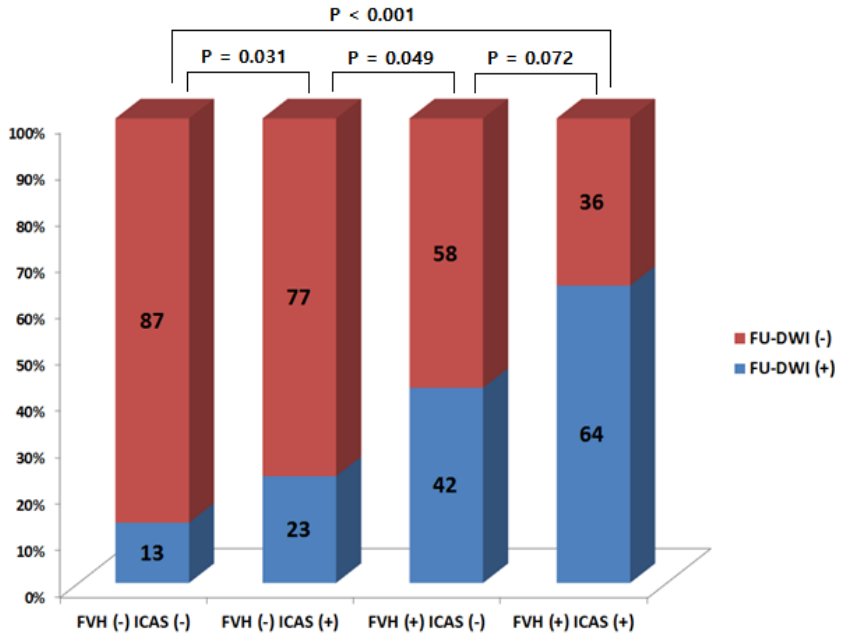
C. Single small subcortical: single subcortical lesion within a size of 20 mm

D. Large perforator: lesions in the territories of the large perforator artery (e.g., striatocapsular infarction, paramedian pontine infarction)

E. Border zone: lesions only between different vascular territory areas

F. Multiple territory: lesions in multiple different vascular territories

Figure 4. Proportions of FU-DWI (+) with and without FVH and ICAS



FU-DWI (+) most frequently occurred in the FVH (+) ICAS (+) group ($P < 0.001$). It decreased according to FVH (+) ICAS (-), FVH (-) ICAS (+), and FVH (-) ICAS (+) in a dose-response manner ($P < 0.001$).

Figure 5. Percentile distributions of patterns of FU-DWI lesions

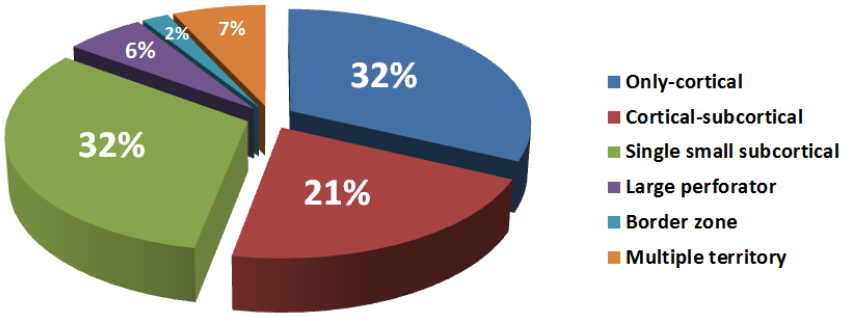
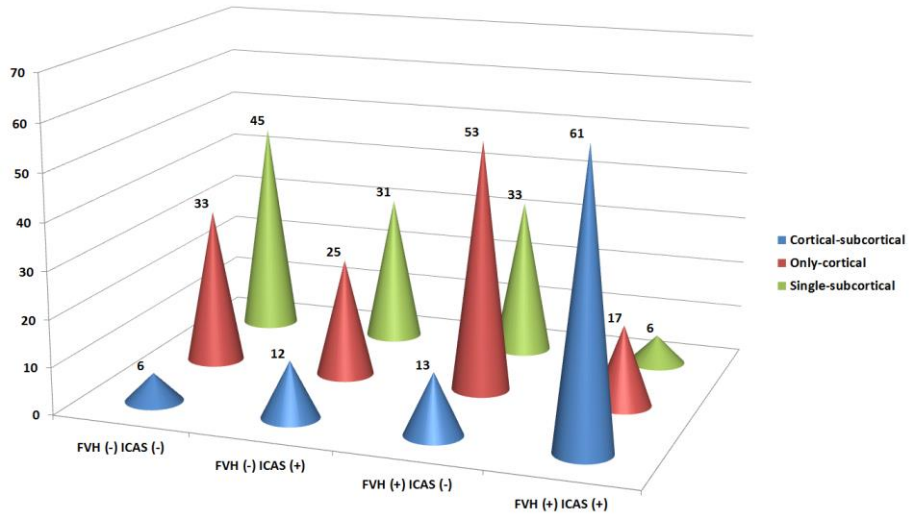
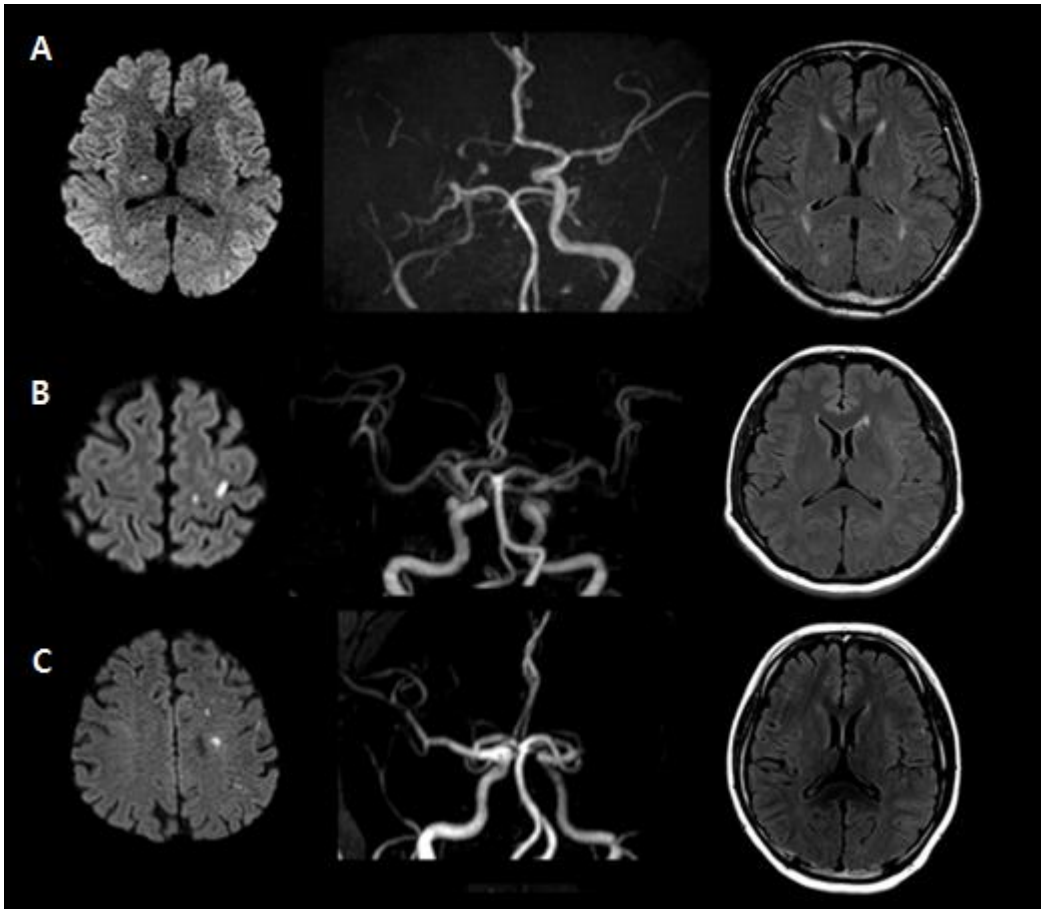


Figure 6. Percentile distributions regarding the patterns of FU-DWI (+) lesions with and without FVH and ICAS



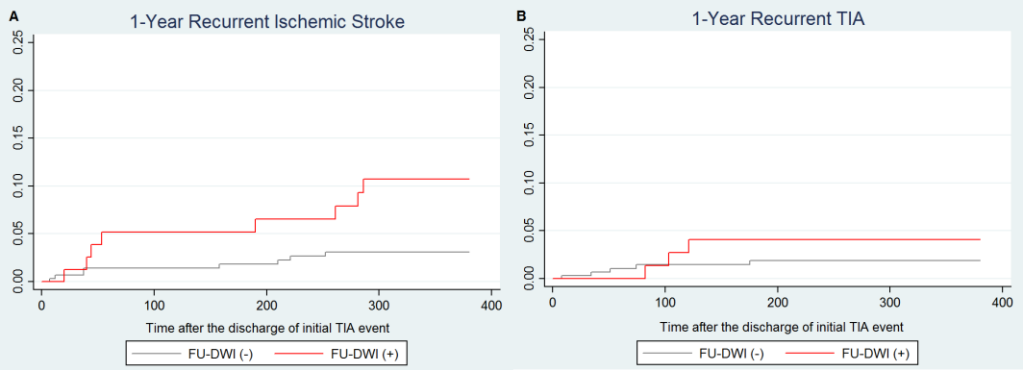
The FVH (+) ICAS (+) group showed the most frequent cortical-subcortical patterns ($P < 0.001$) and the least single small subcortical pattern ($P < 0.001$). The only-cortical pattern was most frequent in the FVH (+) ICAS (-) group; however, it was not statistically significant.

Figure 7. Representative cases with and without FVH and ICAS



A. FVH (-) ICAS (+) group: initial fluid attenuated inversion recovery (FLAIR) imaging showed no significant lesion, magnetic resonance angiography (MRA) showed an intracranial atherosclerosis (ICAS) lesion on right M1 artery, and follow-up diffusion weighted imaging (DWI) presented a single small subcortical lesion pattern in the right basal ganglia.
B. FVH (+) ICAS (-) group: initial FLAIR imaging showed FLAIR vascular hyperintensity (FVH) on left middle cerebral artery area, MRA indicated no significant lesion, and follow-up DWI presented an only-cortical lesion pattern in the left frontal cortex.
C. FVH (+) ICAS (+) group: initial FLAIR imaging showed FVH on middle cerebral artery area, MRA showed ICAS on left M1 artery, and follow-up DWI presented a cortical-subcortical lesion pattern in the left middle cerebral artery area.

Figure 8. Recurrent transient ischemic attack or ischemic stroke after discharge between FU-DWI (+) and FU-DWI (-) groups



A. The FU-DWI (+) group showed a higher rate of 1-year recurrent ischemic stroke than the FU-DWI (-) group (P = 0.007). B. Recurrent TIAs were not different between the groups (P = 0.290).

국문 초록

일과성 허혈 발작은 신경과적 응급 상황으로, 이후 신경학적 후유증을 남길 수 있는 허혈성 뇌경색을 동반 할 수 있는 주요한 질환이다. 현재 일과성 허혈 발작의 진단은 대부분 환자의 병력에 의거해 진단을 하고 있는 상황이며, 이로 인해 많은 유사질환 (발작, 편두통, 저혈당, 정신과적 질환)과의 감별이 어려워 그 정확한 예후에 대해 예측하기 어렵다. 초기 자기 공명 영상에서 병변이 보이는 일과성 허혈 발작 환자의 경우 그 진단에 있어 용이하나, 진료 현장에 있어서 많은 부분을 차지 하는 병변이 보이지 않는 환자의 경우 진단을 위한 객관적인 지표를 요하고 있다. 이들 환자군에 대해 초기에 추적 (Follow-up) 자기 공명 영상을 촬영하는 방법도 도움이 되겠으나, 이러한 방법을 임상에서 항상 사용할 수 있는 것은 아니다.

유체 감쇠 반전 복구 영상 (FLAIR)의 혈관 고강도 신호는 대혈관 폐색시 곁순환이 자기 공명 영상을 통해 나타나는 것으로, 일과성 허혈 발작도 중추 신경계의 혈관 폐색으로 인한 질환임을 생각했을 때, 일과성 허혈 발작 발생시 일시적으로 FLAIR 혈관 고강도 신호가 나타날 수 있다. 따라서 이 연구에서는 초기 자기 공명 영상에 병변이 없는 일과성 허혈 발작 환자에서 FLAIR 혈관 고강도 신호와 추적 영상의 병변

사이의 관계를 통해 이들 환자군에서 보다 객관적이고 간단한 예측 지표를 찾고자 한다.

2010 년에서 2015 년 사이에 서울대학교 병원 및 서울대학교 분당 병원에 일과성 허혈 발작을 주소로 내원한 사람 중, 증상 발생 후 24 시간 이내에 도착하였으며 추적 자기 공명 영상을 촬영한 환자군을 대상으로 하여 분석하였다. FLAIR 혈관 고강도 신호는 유체 감쇠 반전 복구 영상에서 뇌 겉질을 따라 국소적 혹은 구불구불한 고강도 신호로 정의하였다. 또한, 초기 추적 영상상의 병변이 있고 없음에 따라 이후 임상 경과에 미치는 영향을 확인하기 위해서 두 군간의 1 년 허혈성 뇌경색 및 일과성 허혈 발작의 재발에 대해서도 비교해 보았다.

총 392 명의 초기 병변이 없는 일과성 허혈 발작 환자를 분석하였으며, 그 중 82 명의 환자에서 추적 영상상의 병변이 발견되었다. 초기 추적 영상상 병변의 예측 인자들에 대한 다변량 분석에서 FLAIR 혈관 고강도 신호는 다른 보정 변수들을 보정한 후에도 유의미하게 독립적인 변수로 남았다 [adjusted OR (aOR) = 4.77, 95% confidence interval (CI) 2.45−9.29, $P < 0.001$]. 그 밖에도 초기 증상 발생 후 자기 공명 영상 촬영까지 걸린 시간 (aOR = 0.49, 95% CI = 0.33−0.70, $P < 0.001$) 과 두개 내 죽상 경화증 (aOR = 2.07, 95% CI

= 1.10−3.92, P = 0.025) 도 FLAIR 혈관 고강도 신호와 독립적인 변수로 남았다. 이후 임상 경과에 있어서, 추적 영상상 병변이 있는 군은 그렇지 않은 군에 비하여 1 년 내 허혈성 뇌경색 재발이 유의하게 많았다 (10.7% versus 3.1%, respectively, P = 0.007).

FLAIR 혈관 고강도 신호는 초기 병변이 없는 일과성 허혈 발작 환자에서 초기 추적 영상 상 병변 발생과 관련이 있었다. 또한 이들 환자군에서 초기 추적 영상 상 병변 재발이 많은 빈도로 발생하였으며, 이러한 재발군에서 퇴원 후 예후도 좋지 않기 때문에 추가적인 영상 및 임상 지표들에 대한 연구가 필요할 것으로 생각된다.

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주요어: 일과성 허혈 발작, 유체 감쇠 반전 복구 영상, 예후, 허혈성 뇌졸중, 재발, 뇌 관류, 곁순환

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