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FLAIR Vascular Hyperintensity Topography, Novel Imaging Marker for Revascularization in Middle Cerebral Artery Occlusion

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Abstract

Background and Purpose—In acute arterial occlusion, FLAIR vascular hyperintensity (FVH) has been linked to slow flow in leptomeningeal collaterals and cerebral hypoperfusion, but the impact on clinical outcome is still controversial. In this study, we aimed to investigate the association between FVH topography or FVH-ASPECTS pattern and outcome in acute M1-MCA occlusion patients with endovascular treatment.

Methods—We included acute M1-MCA occlusion patients treated with endovascular therapy. All patients had DWI and FLAIR before endovascular therapy. Distal FVH ASPECT score was evaluated according to distal MCA-ASPECT area (M1–M6) and acute DWI lesion was also reviewed. Presence of FVH inside and outside DWI positive lesions was separately analyzed. Clinical outcome after endovascular therapy was analyzed with respect to different distal FVH-ASPECTS topography.

Results—Among 101 patients that met inclusion criteria for the study, mean age was 66.2±17.8 and median NIHSS was 17.0 (IQR 12.0–21.0). FVH-ASPECTS measured outside of the DWI lesion was significantly higher in patients with good outcome (mRS 0–2), (8.0 vs 4.0, p<0.001). Logistic regression demonstrated that FVH-ASPECTS outside of the DWI lesion was independently associated with clinical outcome of these patients (OR 1.3; 95% CI, 1.06 to 1.68;

p=0.013). FVH-ASPECTS inside the DWI lesion was associated with hemorrhagic transformation (OR 1.3; 95% CI, 1.04 to 1.51; p=0.019).

Conclusions—Higher FVH-ASPECTS measured outside the DWI lesion is associated with good clinical outcomes in patients undergoing endovascular therapy. FVH-ASPECTS measured inside the DWI lesion was predictive of hemorrhagic transformation. The FVH pattern, not number, can serve as an imaging selection marker for endovascular therapy in acute middle cerebral artery occlusion.

Keywords

ischemic stroke; revascularization; imaging; magnetic resonance imaging

Introduction

Advanced imaging method was an essential component of recently clinical trials' success in support of mechanical thrombectomy for acute ischemic stroke with large artery occlusion[1, 2]. ASPECT scoring is a validated method for assessing tissue status with either CT or MR imaging[3] and improved collateral flow was associated with improved imaging and clinical outcomes in patients undergoing acute endovascular therapy[4]. Then, finding an easy and reproducible ASPECT collateral scoring that reflects both tissue and vascular status can extend this opportunity to more patients at greatest risk of long-term disability.

FLAIR vascular hyperintensity (FVH), which represents slow blood flow in leptomeningeal collaterals[5, 6], can provide a direct and non-invasive visualization of collateral pathways[7–9]. As to the prognostic value of FVHs, the results of different studies[7, 10–12] lack consensus. These discrepancies might be explained by difference among populations, end points, and FVH classifications[13]. However, we found that all these studies focused solely on the presence or number of FVHs, rather than the topography or pattern of FVHs. Furthermore, the juxtaposition of FVH relative to established DWI lesions indicative of core infarction may be linked with subsequent imaging and clinical outcomes.

The purpose of this study was to prospectively assess the association between FVH-ASPECTs pattern or topography and the outcome of patients with acute middle cerebral artery (MCA) occlusion.

Patients and Methods

Patients and Clinical Assessment

We prospectively evaluated consecutive patients who received endovascular therapy (ET, intra-arterial thrombolytic therapy or mechanical thrombectomy) for acute cerebral ischemia between September 2004 and December 2014. Patients were included in our study if they had initial imaging demonstrating occlusion of proximal M1 segment of the MCA, and underwent conventional angiography for consideration of ET. The patients were excluded if they didn't undergo MRI scan or the imaging couldn't be analyzed. Patients were also excluded if tandem vessel occlusions (ie, ICA+MCA) were identified. Finally, 101 patients were included in the analysis. Demographic, clinical and laboratory data were retrieved from

a prospectively maintained, single center dataset of consecutive cases. The following stroke risks factors were identified: age, sex, hypertension, diabetes, hyperlipidemia, previous stroke/ transient ischemic attack (TIA), coronary artery disease (CAD), chronic heart failure (CHF), and arterial fibrillation (AF). Baseline characteristic, including NIHSS, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, cholesterol and previous medications were also collected from these patients.

Imaging Analysis

All patients' imaging data were reviewed at UCLA Neurovascular Imaging Research Core by two authors (D.L and W.S). All MRI studies included diffusion-weighted imaging (DWI) and FLAIR. DWI lesion volume measurement was performed by one of the authors (F. S) blinded to the clinical information using a computer-assisted volumetric analysis program (Olea Medical, La Ciotat, France). Diffusion was measured at three values of b (b=0, 500, 1000 s/mm^2), and average apparent diffusion coefficient (ADC) maps were generated. DWI volumes were quantified from analysis of isotropic b1000 images and ADC maps with threshold of ADC<600. Determination of M1 occlusion was made by review of angiographic images. Hemorrhagic transformation (HT) was defined as a new hyperattenuated region identified on any follow-up CT scan before patient discharge, as previously described[14]. In all cases, angiography was performed subsequent to the initial MRI study.

FVH were defined as focal, tubular, or serpentine hyperintensities in the subarachnoid space relative to CSF and corresponding to the typical arterial course[5]. As shown in Figure 1, Total FVH-Alberta Stroke Program Early CT Score (FVH-T-ASPECTS) was assessed according to distal MCA-ASPECTS area (M1–M6). FVH in every distal MCA-ASPECTS area was separately evaluated. For example, no FVH in M1 area was recorded as 0, less than M1 half area was recorded as 1, more than M1 half area was recoded as 2. Those distal MCA-ASPECTS areas were defined as DWI-positive area if there was acute infarction lesion in the areas. FVH-ASPECTS score outside DWI-positive area (FVH-O-ASPECTS) and FVH-ASPECTS inside DWI-positive area (FVH-I-ASPECTS) were separately analyzed. Then, FVH-I-ASPECTS was graded as subtle FVH-I-ASPECTS (0–2 points) and prominent FVH-I-ASPECTS (>2 points). Similarly to that, FVH-O-ASPECTS was graded as subtle FVH-O-ASPECTS (0–4 points) and prominent FVH-O-ASPECTS (>4 points).

Angiographic collateral grade was evaluated with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System on baseline angiography. Collateral rating was performed by one author (D.S.L) with extensive experience in angiographic interpretation in acute stroke, blinded to the clinical presentation and outcomes. Dichotomization was then performed by dividing into groups of 0–2 vs 3–4. Assessment of vascular recanalization was based on the Thrombolysis in Cerebral Infarction (TICI) scale.

Statistical analysis

Continuous variables with a normal distribution were described as mean±SD and non-normally distributed variables were described as median and interquartile range. We

compared continuous variables using the Student *t* test or Mann-Whitney *U* test, as appropriate. Categorical variables were compared using Pearson χ^2 or Fisher exact test, as appropriate. Logistic regression analyses were done to determine the independent predictors of favorable clinical outcome and HT. All covariates with a *P* value 0.1 in a univariate analysis were entered into this logistic regression model and a value of P<0.05 was used to indicate statistical significance.

Results

The main baseline characteristics of the patients are summarized in Table 1 and Figure 2. During this period, 101 acute ischemic stroke patients with MCA-M1 occlusion were included in our study. Among these patients, 29 (28.7%) patients were male and the average age was 66.2±17.8 years. 6 patients were treated with IA tPA, 49 patients were treated with Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device, 20 patients were treated with Solitaire device, 26 patients were treated with other methods (including Penumbra device, mechanical disruption, angioplasty and all complex methods). Median baseline NIHSS score was 17 [range 12–21] and median FVH-T-ASPECTS score was 9 [range 5–10]. 98 (98/101, 97.0%) patients have FVH on the FLAIR imaging. FVH were facing the M2, M5, M3, M6, M4, and M1 ASPECTS regions in 97%, 83%, 73%, 56%, 54%, and 46% of patients, respectively (average of 2 readers). The distribution of FVH-T-ASPECTS score in different ASPECT areas was also shown in Figure 2.

FVH-O-ASPECTS score and FVH-I-ASPECTS score

The interobserver agreement for FVH-T-ASPECTS was $k = 0.72$ (95% CI, 0.62–0.81), for FVH-O-ASPECTS was $k = 0.71$ (95%, CI 0.61–0.80) and for FVH-I-ASPECTS was $k = 0.74$ (95% CI, 0.65–0.83). In our study, subtle FVH-O-ASPECTS score were observed in 49 patients (48.5%) and prominent FVH-O-ASPECTS score were observed in 52 patients (51.5%). As shown in Table-1, subtle FVH-O-ASPECTS has a higher baseline NIHSS score (19.0 vs 14.5, p=0.016), lower baseline cholesterol (149.1±38.1 vs 167.0±48.9, p=0.043), larger infarct volume (46.5 vs 13.7, p=0.001), and more patients with lower ASITN score (73.5% vs 48.1%, p=0.009). The number of patients with a favorable clinical outcome was also smaller in subtle FVH-O-ASPECTS group than prominent FVH-O-ASPECTS group (6.1% vs 30.8%, p=0.002). As to HT, there was no difference in these two groups (38.8% vs 25.0%, p=0.137).

As shown in the details of Table 1, 101 patients were graded as subtle FVH-I-ASPECTS group (64/101, 63.4%) and prominent FVH-I-ASPECTS group (37/101, 36.6%). Compared to prominent FVH-I-ASPECTS group, subtle FVH-I-ASPECTS group has a lower baseline NIHSS score (13.5 vs 20.0, p=0.001), smaller infarct volume (13.0 vs 65.0, p<0.001), and less patients with low ASITN score (51.6% vs 75.7%, p=0.017). More patients in subtle FVH-I-ASPECTS group had a good clinical outcome than prominent FVH-I-ASPECTS group (26.6% vs 5.4%, p=0.009). Patient in subtle FVH-I-ASPECTS group also had less hemorrhagic transformation after endovascular therapy (23.4% vs 45.9%, p=0.019).

Clinical and Imaging Outcomes

Variables associated with a favorable clinical outcome are shown in Table 2. Patients' age (p=0.013), history of diabetes (p=0.078), baseline NIHSS score (p<0.001), FVH-O-ASPECT score (p<0.001), FVH-I-ASPECT score (p=0.009), infarct volume (p=0.006), oTICI score (p=0.015), and HT (p=0.006) were included in our analysis. After adjusting for representative variables, higher FVH-O-ASPECTS (OR 1.3; 95% CI, 1.06 to 1.68; p=0.013) appeared as independent predictors of favorable outcome (shown in Figure 3).

As shown in Table 2 and Figure 4, 32 patients (32/101, 31.7%) had hemorrhagic transformation after endovascular therapy. Although higher baseline NIHSS score (p=0.012), higher blood glucose (p=0.016), history of anticoagulation therapy (p=0.066), higher FVH-I-ASPECTS (p=0.016), infarct volume (p=0.010), and lower ASITN score (p=0.041) were related to hemorrhagic transformation in univariate analysis, in the multivariate analysis, only history of anticoagulation therapy (OR 4.7; 95% CI, 1.26–17.12; p=0.021) and higher FVH-I-ASPECTS (OR 1.3; 95% CI, 1.04 to 1.51; p=0.019) emerged as independent predictors of hemorrhagic transformation.

Discussion

Our novel results demonstrate that the number of distal FVH-ASPECTS have no prognostic value in acute MCA occlusion patients undergoing endovascular therapy, yet FVH topography is key. Distal FVH-ASPECTS measured outside the DWI lesion is associated with good clinical outcomes. In addition, distal FVH-ASPECTS measured inside the DWI lesion is predictive of hemorrhage transformation. FVH topography and juxtaposition to DWI lesions, not number, can serve as an imaging selection marker for endovascular therapy in acute middle cerebral artery occlusion.

FVH is related with a higher grader of collateral circulation distal to large-vessel stenosis or occlusion[6], and the presence of FVH ranges from 45% to 100% in stroke patients with intracranial arterial occlusion[7, 8]. In the present study, we included patients with proximal MCA occlusion and all of them were imaged within a short time, which can explain the high prevalence of FVH (97%). In addition to the high prevalence of FVHs, the distribution of the FVHs in our study is also similar to the previous study[13]. As we know, the underlying mechanism involved in the FVH presence is a slow blood flow through the leptomeningeal collaterals[5, 15, 16]. After proximal MCA occlusion, leptomeningeal collaterals from ACA or PCA open and the blood pressure falls when moving from borderzone areas (M1, M6) to more proximal areas (M2, M5). Then, it may be the reason why more FVHs were observed in M2 area than M1 area in our study, which is also proved by the previous studies[13, 17].

The prognostic value of FVHs has been widely investigated by previous studies[7, 8, 18], and discrepancies have been attributed to differences among populations, imaging time and FVH classifications. Similar to the previous study[10], our study got the result that total FVHs within MCA territory had no prognostic value. However, we found that FVHs outside DWI lesion had a good prognostic value in patients with acute proximal MCA occlusion. Extent of FVHs was associated with the presence of a PWI-DWI mismatch[19, 20], and FVHs beyond the DWI lesion represent markedly impaired hemodynamics[13]. More FVHs outside DWI

lesion mean larger amounts of tissue at risk of infarct expansion. Then, after acute MCA occlusion, patients with more FVHs beyond DWI lesion may benefit better clinical recovery because recanalization of occlusion artery can save at-risk tissue.

Hemorrhagic transformation, the major complication of endovascular therapy, is associated with increased stroke morbidity and mortality[21]. Several brain imaging approaches, including MRI enhancement patterns, T2*-permeability MRI[22], apparent diffusion coefficient[23] and very low cerebral blood volume[24], have been evaluated to predict HT after stroke. Furthermore, collateral circulation has also been associated with HT in patients where recanalization occurs[25]. In the present study, we found that FVHs inside DWI lesion was associated with HT in acute MCA occlusion. As we know, ROS and blood-derived factors MMP-9 have emerged as important mediators in early HT[21]. Within 30minutes of focal cerebral ischemia, ischemic stroke elicits a robust activation of the immune system and circulating leukocytes adhere to vascular endothelial cells[26]. More FVHs inside DWI lesion means that more circulating leukocytes can move to ischemic area through leptomeningeal collaterals. Then, leukocytes adhesion and migration across the vasculature can activate a number of signaling cascades that increase the BBB permeability[26].

The present study has some limitations. First, this is a hospital-based clinical study of moderate size. However, to our knowledge, this is the first study that analyzes FVHs pattern involving FVHs distribute inside DWI lesion. Further multicenter studies are needed to confirm our findings. Second, based on the consideration of patient homogeneity, we only included patients with acute MCA occlusion. Acute MCA stroke without MCA occlusion are not analyzed in the present study, which can be analyzed in the future study. Third, perfusion imaging was not available for all these patients. However, previous study has demonstrated that FVH beyond the DWI lesion represent the ischemic penumbra. Then, more FVHs distributing outside the DWI lesion means that more tissue at risk can be saved by endovascular therapy.

Conclusions

Acute MCA occlusion patients with more FVHs (FVH-ASPECTs >4) outside DWI lesion and less FVHs (FVH-ASPECTs 2) inside DWI lesion have better outcome after endovascular therapy. Then, FVHs pattern can provide as a novel imaging criteria for patient selection of endovascular therapy.

Acknowledgments

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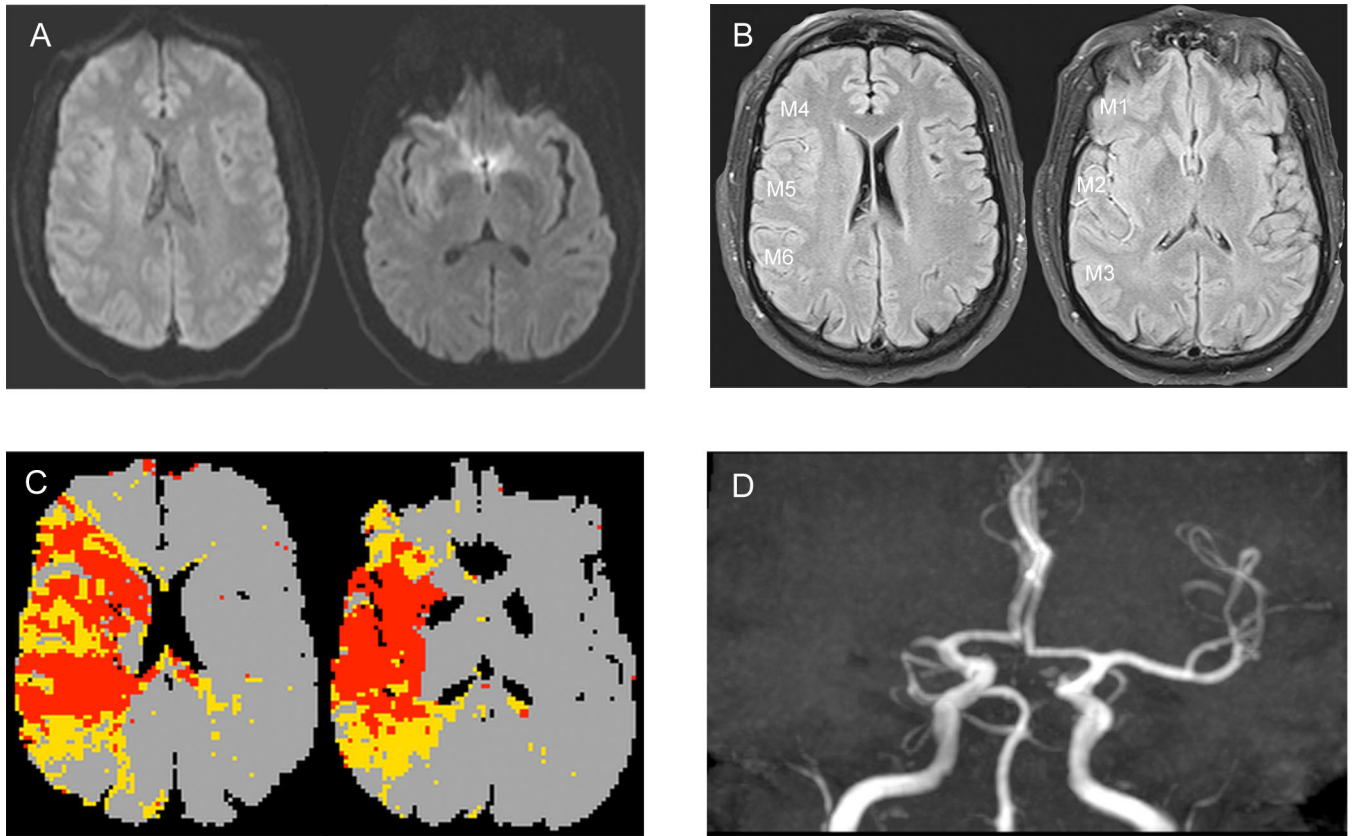
Figure 1.
Illustrative case of FVH-ASPECTS evaluation in a patient with a right MCA occlusion (A–D). No hyperintense lesions are visible in the right MCA territory (A). FVH-T-ASPECT score was 11 (M1=1, M2=2, M3=2, M4=2, M5=2, M6=2), FVH-O-ASPECTS was 11 and FVH-I-ASPECTS was 0 (B). PWI showed that mismatch on the Tmax map was congruent with the FVHs distribution(C).
Abbreviations: FVH-T-ASPECTS=total FVH-ASPECT score, FVH-O-ASPECTS=FVH-ASPECT score outside DWI-positive area, FVH-I-ASPECTS=FVH-ASPECT score inside DWI-positive area
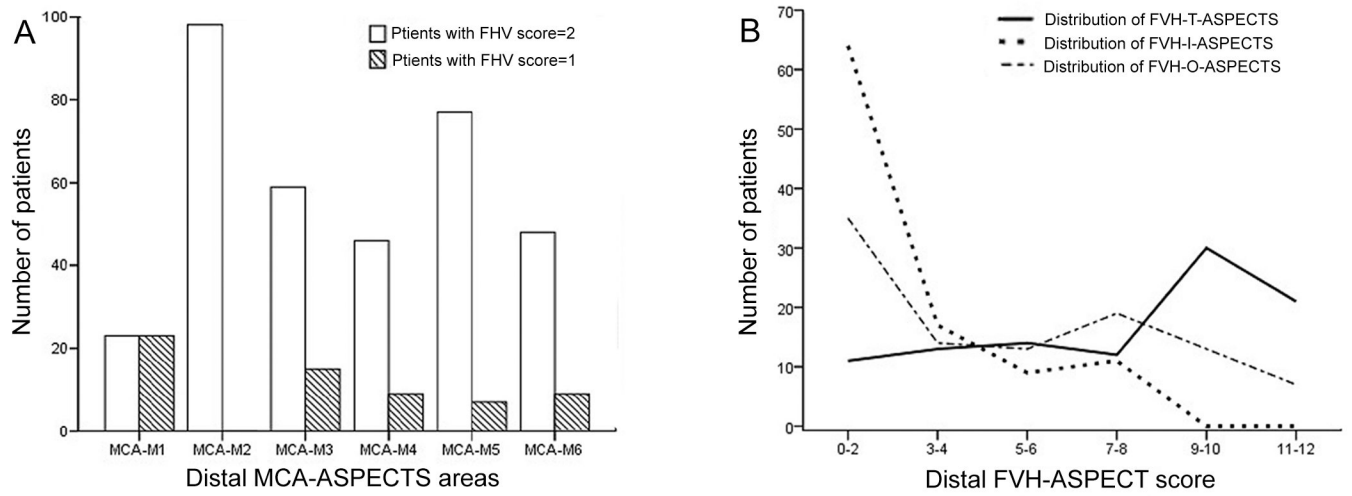
Figure 2.

Location and frequencies of FVH according to the surface of distal ASPECT territories.

A. Number of patients with FVHs in different ASPECT area.

B. Number of patients according to different FVH distribution.

Figure 3.
Representative case of prominent FVH-O-ASPECTS.
A 46-years-old man with a right MCA occlusion and NIHSS of 13 on admission (A–D).
Baseline total FVH-ASPECT score (B) was 11 (FVH-O-ASPECTS=9 and FVH-I-ASPECTS=2). After recanalization of the right MCA, FVH-ASPECTS decreased to 2 and no hemorrhagic transformation was found on the images (arrows on B and C). Discharge mRS of this patient was 1.
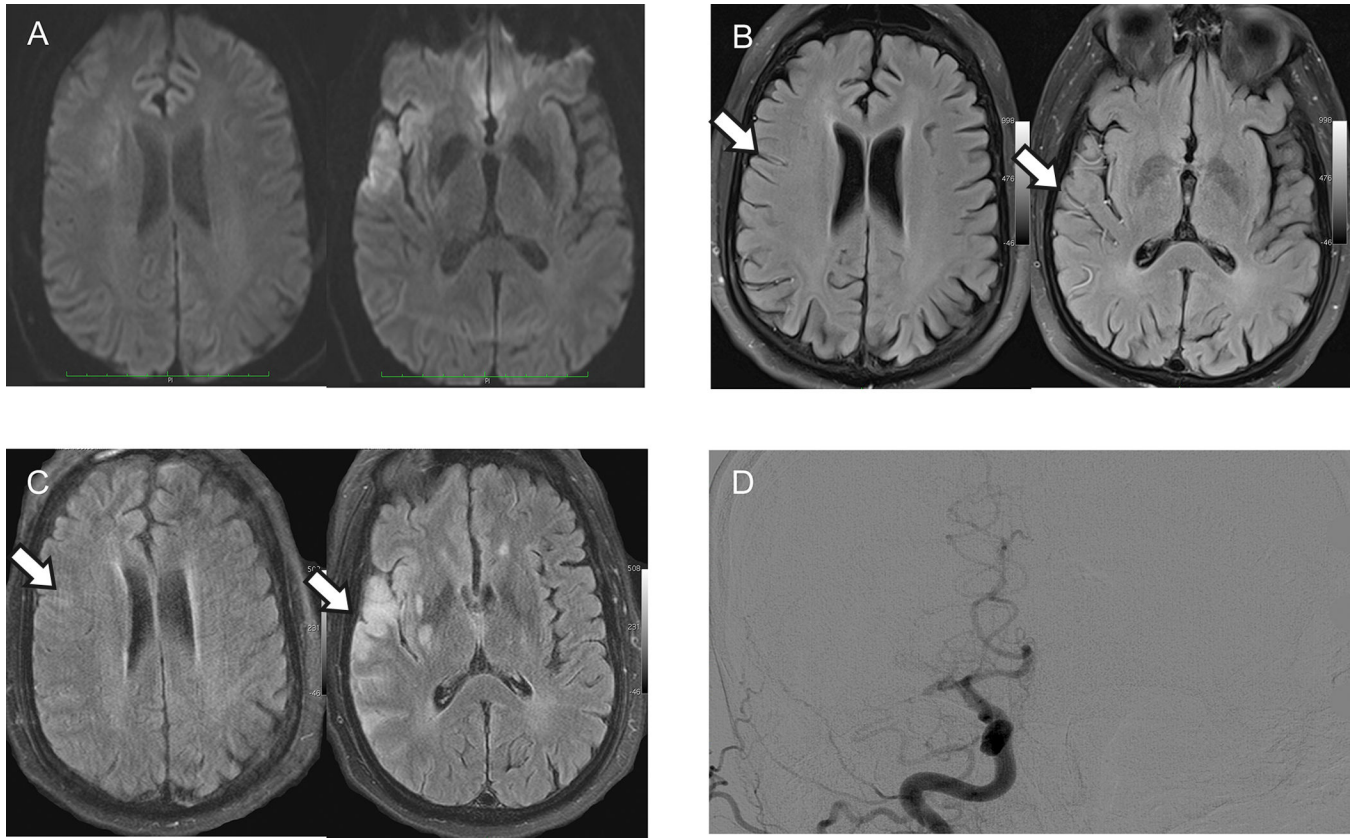
Figure 4.

Representative case of prominent FVH-I-ASPECTS.
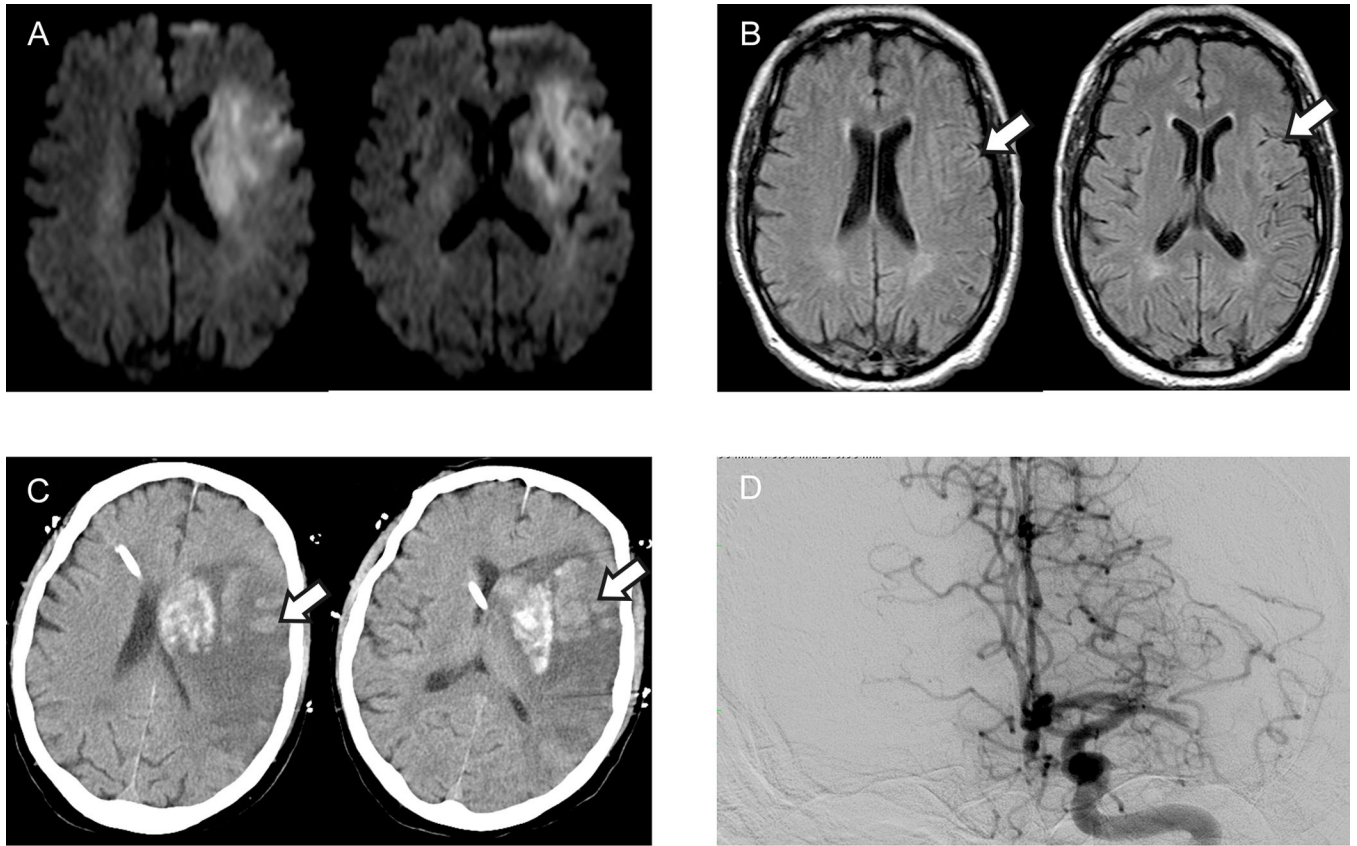
A 70-years-old man with a left MCA occlusion and NIHSS of 30 on admission (A–D). Baseline total FVH-ASPECT score (B) was 10 (FVH-O-ASPECTS=5 and FVH-I-ASPECTS=5). Hemorrhagic transformation was found on the follow-up CT after recanalization (C). The hematoma shape was similar to FVH-I-ASPECTS distribution (arrows on B and C) and this patient died 4 days after admission.

Table 1

Baseline characteristics in patients with different FHV-ASPECTS

Characteristics	Subtle FVH-O-ASPECTS (n=49)	Prominent FVH-O-ASPECTS (n=52)	p Value	Subtle FVH-I-ASPCTS (n=64)	Prominent FVH-I-ASPECTS (n=37)	p Value
Age, (mean±SD)	68.2±17.3	64.3±18.2	0.269	66.0±18.6	66.4±16.7	0.925
Male, n(%)	13(26.5)	16(30.8)	0.638	17(26.6)	12(32.4)	0.530
Risk factors						
Hypertension, n(%)	35(71.4)	35(67.3)	0.654	44(68.8)	26(70.3)	0.873
Diabetes, n(%)	10(20.4)	10(19.2)	0.882	12(18.8)	8(21.6)	0.727
Hyperlipidemia, n(%)	16(32.7)	19(36.5)	0.682	21(32.8)	14(37.8)	0.609
Stroke/TIA, n(%)	7(14.3)	2(3.8)	0.086	7(10.9)	2(5.4)	0.347
CAD, n(%)	8(16.3)	9(17.3)	0.895	12(18.8)	5(13.5)	0.498
CHF, n(%)	7(14.3)	3(5.8)	0.152	8(12.5)	2(5.4)	0.250
AF, n(%)	23(46.9)	23(44.2)	0.785	30(46.9)	16(43.2)	0.724
Initial NIHSS	19.0(13.0–23.0)	14.5(11.0–19.8)	0.016*	13.5(10.0–19.8)	20.0(15.5–23.0)	0.001*
SBP mmHg, median (IQR)	156.4±35.5	151.9±32.2	0.511	154.2±35.5	153.8±34.7	0.960
DBP mmHg, median (IQR)	89.0±22.9	84.9±17.4	0.314	87.3±20.2	86.3±20.6	0.815
Blood glucose, mM, median (IQR)	132.5±52.1	132.3±38.9	0.983	127.4±39.9	140.9±53.5	0.154
Cholesterol, mM, median (IQR)	149.1±38.1	167.0±48.9	0.043*	164.7±45.5	147.2±41.6	0.059
Previous medications						
Antiplatelet therapy, n(%)	13(26.5)	10(19.2)	0.382	14(21.9)	9(24.3)	0.777
Anticoagulation therapy, n(%)	6(12.2)	7(13.5)	0.855	11(17.2)	2(5.4)	0.088
Right side	23(46.9)	28(53.8)	0.488	34(53.1)	17(45.9)	0.487
TOTAL FVH -ASPECTS	5.0(3.0–8.0)	10.0(9.0–11.0)	<0.001*	7.5(4.0–10.0)	9(7.0–12.0)	0.001*
Infarct Volume	46.5(14.6–89.6)	13.7(6.3–33.7)	0.001*	13.0(5.9–23.7)	65.0(30.5–97.5)	<0.001*
ASITN (0–2)	36(73.5)	25(48.1)	0.009*	33(51.6)	28(75.7)	0.017
oTICI (0–2a)	36(73.5)	26(50.0)	0.015	39(60.9)	23(62.2)	0.903
IV t-PA	23(46.9)	20(38.5)	0.389	28(43.8)	15(40.5)	0.753
ET methods			0.789			0.818
IA tPA	3(6.1)	3(5.8)		3(4.7)	3(8.1)	
MERCI	26(53.1)	23(44.2)		33(51.6)	16(43.2)	

Characteristics	Subtle FVH-O-ASPECTS (n=49)	Prominent FVH-O-ASPECTS (n=52)	p Value	Subtle FVH-I-ASPCTS (n=64)	Prominent FVH-I-ASPECTS (n=37)	p Value
Solitaire	8(16.3)	12(23.1)		12(18.8)	8(21.6)	
Other methods	12(24.5)	14(26.9)		16(25.0)	10(27.0)	
HT	19(38.8)	13(25.0)	0.137	15(23.4)	17(45.9)	0.019*
Discharge mRS 2	3(6.1)	16(30.8)	0.002*	17(26.6)	2(5.4)	0.009*

Abbreviations: FVH-O-ASPECTS=FVH-ASPECTS score outside DWI-positive area; FVH-I-ASPECTS= FVH-ASPECTS inside DWI-positive area; TIA= transient ischemic attack; CAD= coronary artery disease; CHF= Chronic heart failure; AF=arterial fibrillation; SBP=systolic blood pressure; DBP= diastolic blood pressure; ET= Endovascular treatment; HT= hemorrhagic transformation.

Table 2

Logistic regression analysis of factors associated with clinical and radiological outcome

Characteristics	mRS 2 (n=19)	mRS>2 (n=82)	p Value	OR	95% CI	P value	Without HT (n=69)	With HT (n=32)	P value	OR	95% CI	P value
FVH-T-ASPECTS	9.0(7.0–11.0)	8.0(4.0–10.0)	0.187				8.0(4.0–10.0)	9.0(5.0–10.0)	0.450			
FVH-O-ASPECTS	8.0(6.0–10.0)	4.0(2.0–8.0)	<0.001	1.335	1.063–1.677	0.013	5.0(2.0–8.0)	4.0(2.0–8.0)	0.293			
FVH-I-ASPECTS	0(0–2.0)	2(0–4.25)	0.009	0.925	0.561–1.524	0.759	1.0(0–3.5)	3.0(0.25–6.0)	0.016	1.250	1.037–1.506	0.019

Abbreviations: FVH-T-ASPECTS = Total FVH-ASPECTS score; FVH-O-ASPECTS=FVH-ASPECTS score outside DWI-positive area; FVH-I-ASPECTS = FVH-ASPECTS inside DWI-positive area; HT= hemorrhagic transformation.