BRIEF COMMUNICATION

Proximal flow to middle cerebral artery is associated with higher thrombus density in terminal internal carotid artery occlusion

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Abstract

Proximal collaterals may determine the composition of occluding thrombi in acute ischemic stroke (AIS) in addition to source, hematocrit, time, and medication. Here, we performed a retrospective study of 39 consecutive patients with radiological evidence of I-, L-, and T-type terminal internal carotid artery occlusion. Middle cerebral artery (MCA) thrombus density was assessed on noncontrast enhanced CT and proximal collaterals on CT angiography. In patients with presence of proximal collaterals to the MCA we detected more hyperdense clots ($P = 0.003$) and a higher frequency of leptomeningeal collaterals ($P = 0.008$). We expand the spectrum of factors that potentially determine clot perviousness and evolution of ischemic stroke.

Introduction

Acute ischemic stroke (AIS) due to occlusion of the terminal internal carotid artery (ICA) is classified as I, L, and T type depending on the involvement of the proximal anterior and middle cerebral artery (MCA).[1] An illustrative 3D reconstruction of CT angiographic images of the variants is shown in Figure 1. Compromised cerebral perfusion, an embolic event, or a combination of hypoperfusion and embolism are the major causes of AIS with ICA occlusion. The condition is associated with poor outcome even with the use systemic thrombolysis, and treatment with mechanical reperfusion strategies remains challenging.[2]

Understanding the composition of the thrombus may provide additional information to determine the potential success of reperfusion efforts and individual prognosis. Several studies confirmed that a higher thrombus density is associated with improved reperfusion rates and better outcome, regardless of systemic or endovascular recanalization techniques.[3–6] Thrombus density can be determined noninvasively on noncontrast enhanced CT (NECT) and was shown to be dependent on source, time, and hematocrit, and is altered by treatment with antiplatelets.[7,8] In patients with ICA occlusion, collateral circulation may play an important role in the severity of ischemic lesions.[9] Here, we evaluated whether proximal

T-Type
ICA+ entire MCA + ACA

L-Type
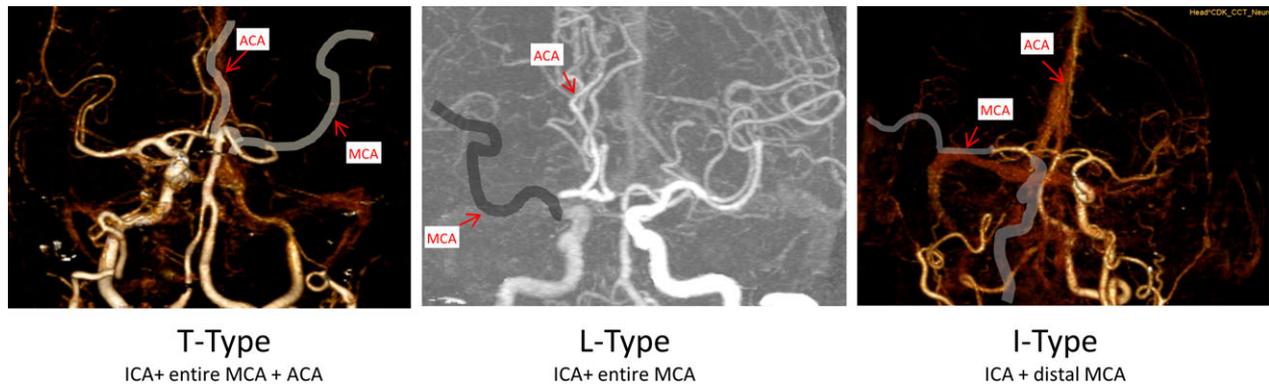ICA+ entire MCA

I-Type
ICA + distal MCA

Figure 1. Illustrative 3D reconstructions of terminal internal carotid artery (ICA) occlusion of T (A), L (B), and I (C) type. The occluded vessels are noted below the images and traced in grey. Legends: Legends:MCA middle cerebral artery, ACA anterior cerebral artery.

collaterals to the MCA in the setting of acute terminal ICA occlusion could be an additional factor determining thrombus density, stroke severity, and clinical outcome.

Methods

We performed a retrospective chart review of all consecutive stroke patients admitted to Christian Doppler Medical Center (Salzburg, Austria, SZ) and University Medical Center Maribor (Slovenia, MB). An ethical approval was not required according to national regulations due to the retrospective study design. The study period was 2012–2016 and the inclusion criteria were ≥18 years of age and terminal ICA occlusion confirmed by CT-angiography (CTA) within 6 h from symptom onset. Brain imaging with

NECT was in all cases followed immediately with CTA. Details of the scanners and imaging protocols were reported previously.[7,8] Cervical ICA occlusion was present if the thrombus extended from the carotid bulb to the level of the petrosal bone. ICA thrombi distal to petrosal bone were regarded as intracranial. The presence of proximal collateral flow to the MCA was assessed on CTA. In detail, CT angiography was examined in three planes (axial, coronary, and sagittal) to assess presence of intravascular contrast material in anterior cerebral artery and MCA. We rated the morphology of carotid artery occlusion as I, L, and T type depending on the involvement of the proximal anterior and MCA.[10] Two examples are shown in Figure 2, Panel A. We used a visual scale to assess the status of leptomeningeal collateralization on CTA.[11] Briefly, the
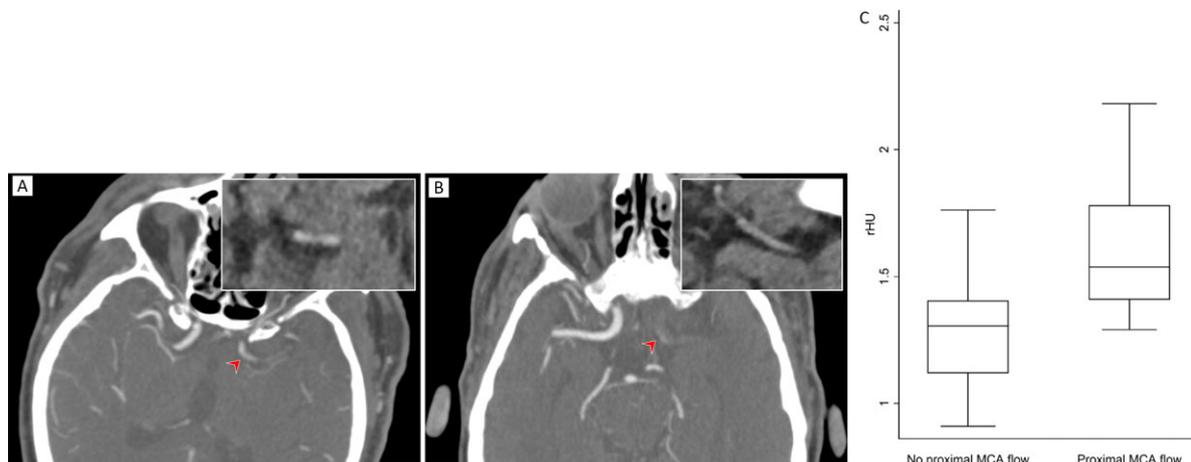

Figure 2. CT angiography in two variants of terminal internal carotid artery (ICA) occlusion. A. Proximal collateral flow to the left MCA, red arrow. B. CTA of a patient lacking proximal collateral flow to the MCA due to extension of the thrombus from the ICA to the MCA, red arrow. The inset depicts the hyperdense MCA on NECT, which is more dense as on image A compared to B. C. Comparison of relative clot density expressed as ratio of density between clot and contralateral vessel (rHU) in the affected MCA based on presence or absence of proximal collateral flow. Box and whisker plot displaying median, 25–75% quartiles, and lowest and highest values.

leptomeningeal collateral pattern was graded by using a three-category ordinal variable (absent, less, or equal to the unaffected contralateral hemisphere). The methods for the determining MCA thrombus characteristics were reported previously.[7,8] Briefly, we quantified density, area, and length of the thrombus on NECT images and confirmed the findings with the CTA results. We calculated relative Hounsfield Units (rHU) as a ratio of ipsilateral and contralateral MCA to correct for hematocrit-related variations. Due to poor visibility of ICA thrombus on NECT, we only characterized the MCA thrombus on NECT and axial plane for density, area, and length. Additional variables included demographic and laboratory data, National Institutes of

Health Stroke Scale (NIHSS) score on admission and at discharge, and infarct volume in cm^3 on follow-up NECT. The statistical analysis was performed with STATA 13.0 (TX, USA) statistical package. We used the nonparametric Kruskal–Wallis test due to nonnormality of continuous data. Categorical variables were examined using the two-tailed Fisher exact test and Pearson $\chi 2$. A level of $P < 0.05$ was considered as statistically significant.

Results

We identified 39 patients with a median age of 76 (interquartile range (IQR) 67–84) and median on admission

Table 1. Clinical and radiological findings of 39 patients with acute terminal ICA occlusion.

Variables	All patients N	All patients Values	I-type occlusion N	I-type occlusion Values	L-/T-type occlusion N	L-/T-type occlusion Values
Age (years)	39	76 (67–84)	8	78 (67–83)	31	75 (67–86)
Men		20 (51.3)		4 (20.0)		16 (80.0)
Women		19 (48.7)		4 (21.1)		15 (78.9)
Admission NIHSS	39	19 (15–23)	8	18 (16–22)	31	19 (14–23)
Discharge NIHSS	26	9.5 (5–16)	7	16 (5–18)	19	9 (4–15)
Hospital Death		14 (35.9)		1 (12.5)		13 (41.9)
Symptom onset to NECT (min)		86 (64–122)		68 (59–79)		92 (64–127)
Average MCA clot density (HU)	39	46.9 (43.1–49.8)		49.0 (44.8–52.2)		46.4 (43.1–49.5)
Ratio clot/nonaffected (rHU)[†]		1.36 (1.18–1.44)		1.53 (1.41–1.78)		1.30 (1.12–1.40)
Hyperdense clot area (mm^2)	37	41.9 (29.8-58.0)	6	44.2 (38.4-49.6)	30	40.2 (28.8–58.0)
Clot length (mm)	39	17.3 (11.9 – 23.5)	7	18.8 (14.4-23.9)	31	16.1 (11.1–23.5)
Level of ICA occlusion						
Cervical		30 (76.9)		7 (87.5)		23 (74.2)
Intracranial		9 (23.1)		1 (12.5)		8 (25.8)
Pattern of pial collaterals						
Absent		16 (41.0)		1 (12.5)		15 (48.4)
Less		18 (46.5)		3 (37.5)		15 (48.4)
Equal		5 (12.8)		4 (50.0)		1 (3.2)
Thrombolysis		29 (74.4)		8 (100.0)		21 (67.7)
Time to thrombolysis	25	120 (90–135)	8	103 (83–137)	15	120 (90–122)
Mechanical thrombectomy		19 (48.7)		4 (50.0)		15 (48.4)
Thrombolysis + thrombectomy		14 (35.9)		4 (50.0)		10 (32.3)
Time to puncture	22	201 (164–239)	5	219 (122–250)	17	198 (167-237)
Time to recanalization	19	295 (247-329)	5	261 (184-386)	14	300 (272-326)
Intervention time	19	86 (46–118)	5	69 (42–118)	14	88 (57–113)
TICI <2b		6 (30.0)		0 (0.0)		6 (37.5)
TICI >=2b		12 (70.6)		4 (100.0)		8 (61.5)
CT outcome						
Infarction		27 (75)		3 (50.0)		23 (79.3)
Hemorrhagic transformation		9 (25)		3 (50.0)		6 (20.7)
Final infarct volume in cm^3	34	86.9 (28.1–223.4)	6	40.8 (28.1–58.9)	28	136.1 (29.4–262.2)
TOAST classification						
Cardioembolic		18 (46.1)		4 (50.0)		14 (45.2)
Large artery atherosclerotic		9 (23.1)		2 (25.0)		7 (22.6)
Undetermined		3 (7.7)		1 (12.5)		2 (7.1)
Unknown		6 (15.4)		0 (0)		6 (19.3)
Dissection		3 (7.7)		1 (12.5)		2 (6.4)

Data are median (range) or count (percent). Statistically significant univariate interactions at $P < 0.05$ are marked with[†]. HU, Hounsfield units; NIHSS, National Institutes of Health Stroke scale score; TOAST, trial of ORG 10172 in acute stroke treatment criteria.

NIHSS score of 19 (IQR 15–23). Statistical analysis of premedication and stroke etiology did not reveal differences between L-/T- and I-type occlusion. There were no differences for prior history of transient ischemic attack, frequency of AF, peripheral artery disease, diabetes mellitus, arterial hypertension, carotid artery stenosis >50%, blood glucose, and total cholesterol between the groups. Additional details of clinical and radiological outcome, intervention, and stroke etiology are shown in Table 1.

The ICA occlusion extended continuously to the MCA in 31 patients (79%, L/T-type), whereas proximal collateral flow to the MCA was present in 8 (21%, I type). We detected more hyperdense clots (Fig. 2C) and a higher frequency of leptomeningeal collaterals in patients with presence of proximal collateral flow to the MCA ($P = 0.003$ and $P = 0.008$, respectively). Abundance of proximal collateral flow to the MCA was not associated with lower final infarct volume ($P = 0.095$). The level of ICA occlusion did not have impact on clot density and outcome parameters.

Discussion

There is emerging evidence that the success of recanalization efforts is largely driven by the structure of the occluding thrombus.[4–6] Indeed, thrombus perviousness as evidenced by higher clot density is strongly associated with recanalization after intravenous recombinant tissue-plasminogen activator (rt-PA) treatment and favorable functional outcome.[3] Our study disclosed that MCA clots in the context of terminal ICA occlusion differ in terms of density based on the presence of proximal collateral flow. Such a proximal collateral flow was present in 21% and the rate was in the range of a previous study (12%).[10] The relevance of proximal and pial (distal) collaterals for clinical outcome in acute stroke is already established.[11] Most importantly, we detected more hyperdense clots and a higher frequency of leptomeningeal collaterals in patients with proximal collateral flow to the MCA. Kim and coworkers showed that in AIS with ICA occlusion, patients with collateral MCA flow had less severe initial stroke symptoms and a better outcome at 3 months than those without.[9] We expand the knowledge of thrombus pathology in this context by disclosing a higher clot density in patients with proximal MCA flow. Proximal collateral perfusion could attenuate the hypercoaguable state, and remove hypodense and less dissolvable components within the thrombus.[12] In turn, this might support the endo- and exogenous fibrinolytic action by improved access of soluble factors to the gaps among adjacent platelets, fibrin filaments, and red blood cells.[13] Whether the increased detection of leptomenigneal collaterals in I-type occlusion is a consequence of proximal MCA collaterals, thrombus perviousness, or an independent process can only be answered with the analysis of larger cohorts. The relevance of clot perviousness for the recruitment of collaterals has not been established so far. Speed of collateral filling also appears to be a variable in determining eventual lesion size in ICA occlusion, independent of extent of collateralization.[14] Further investigation, especially with catheter angiography, could clarify this variable.[15] In addition, the lack of differences in final infarct volume and clinical outcome may be partly attributed to the small sample size in the I-type occlusion group and range of periprocedural variables. The retrospective study design, use of different scanners, and slice thickness for NECT (3 mm in MB and 4 mm in SZ) are the main shortcomings of our study.

Taken together, we add presence of proximal collateral flow to the factors potentially influencing clot perviousness and distal collaterals in terminal ICA occlusion. Further research elucidating the multifaceted mechanisms involved in thrombus generation and susceptibility to pharmacological and mechanical recanalization strategies is warranted.

Author Contribution

Concept and design (SP, JM, JS), acquisition of data (SP, JM, MKO, CF, HFM, LH) analysis (SP, JM, JS) and interpretation of data (SP, JM, MRM, LH, JS), drafting the article (SP, JS) or revised it critically for important intellectual content (JM, MKO, CF, HFM, LH), and approval of the version to be published (SP, JM, MKO, CF, LH, HFM, MRM, JS).

Conflicts of Interests

None relevant to article.

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