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ORIGINAL COMMUNICATION

Determining factors of better leptomeningeal collaterals: a study of 857 consecutive acute ischemic stroke patients

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Abstract

Background In acute ischemic stroke (AIS) collaterals correlate with infarct size, recanalization rate and clinical outcome. We aimed to identify factors associated with better collateral status in a large series of AIS patients with middle cerebral artery (MCA) occlusion.

Methods In the Acute STroke Registry and Analysis of Lausanne (ASTRAL) from 2003 to 2016, we identified all consecutive AIS with proximal MCA occlusion on CT-angiography performed < 24 h. Collaterals were scored from 0 (absent) to 3 (≥ 100%) and related to multiple demographic, clinical, metabolic and radiological variables in a multivariate regression analysis (MVA).

Results The 857 included patients had a median age of 72.3 years, 48.4% were female and median admission NIHSS was 16. Better collaterals were associated with younger age (OR 0.99; 95% CI 0.98–1.00), hemineglect (OR 1.35; 95% CI 1.03–1.76), absence of visual field defects (OR 0.64; 95% CI 0.46–0.90), eye deviation (OR 0.58; 95% CI 0.43–0.79) and decreased vigilance (OR 0.62; 95% CI 0.44–0.88). Better collaterals were also associated with dyslipidemia (OR 1.57; 95% CI 1.16–2.13), no previous statin use (OR 0.69; 95% CI 0.50–0.95), and lower creatinine levels (OR 0.99; 95% CI 0.99–1.00). On neuroimaging, better collaterals related to higher ASPECTS score (OR 1.27; 95% CI 1.20–1.35) and higher clot burden score (OR 1.09; 95% CI 1.03–1.14).

Conclusions Younger age, dyslipidemia and lower creatinine levels were predictors of better collaterals in AIS patients from proximal MCA occlusions. Greater degree of collaterals related to lower stroke severity on admission. On neuroimaging, better collaterals were independently associated with minor early ischemic changes and lower clot burden. These data may add knowledge on pathophysiology of collaterals development and may help to identify patients with better collaterals for late or aggressive recanalization treatments.

Keywords Acute ischemic stroke · Collateral circulation · Computed tomography-angiography (CTA) · Acute neuroimaging

Abbreviations

AIS	Acute ischemic stroke
CBS	Clot burden score
MCA	Middle cerebral artery

Introduction

Leptomeningeal arterial collaterals are pre-existing anastomoses that cross-connect a small number of distal arterioles of the cerebral arteries [1]. They provide alternative blood flow to support brain viability when a primary vessel in the cervico-cephalic arteries is critically stenosed or occluded, such as in acute ischemic stroke (AIS). A

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greater degree of collaterals at baseline has been associated with smaller infarct size [2], improved recanalization rate after endovascular treatment [3] and improved clinical outcome [4, 5].

The magnitude of collateral flow varies greatly between patients. Still, studies examining determinants of this variability are lacking. Besides genetic and environmental factors, statin use has been associated with good collaterals [6], whereas a history of hypertension and higher systolic blood pressure on admission have been associated with poor collateral status at baseline [7]. Recently, the presence of metabolic syndrome, hyperuricemia and aging were found as independent predictors of poor leptomeningeal collateral status [8]. Malik et al. confirmed the association between poor collaterals and older age, but did not find a favourable influence of pre-stroke statin use on the patency of collateral circulation [9].

The main aim of our study was to investigate factors associated with the degree of leptomeningeal collateral status in a large cohort of AIS patients. In particular, we performed a comprehensive analysis of a large number of possibly associated variables, including demographic, clinical, biochemical, and radiological variables, to identify independent predictors of better collaterals in the acute phase of stroke.

Methods

Patient selection

All consecutive patients included in the Acute STroke Registry and Analysis of Lausanne (ASTRAL) from January 2003 to June 2016 were considered for this study. ASTRAL is a single-center prospective cohort of all AIS patients admitted to the Stroke Center of Lausanne University Hospital within 24 h of an ischemic stroke [10]. It incorporates detailed clinical and laboratory data and multimodal brain imaging techniques. The type and definition of collected variables in ASTRAL is prespecified, and the current analysis was retrospective.

For patient selection, we used the following inclusion criteria: AIS involving the middle cerebral artery (MCA); CT-based multimodal imaging performed < 24 h of last proof of good health; availability of a CT-angiography (CTA) of good quality showing occlusion of the proximal segments (M1 and/or proximal M2), with or without added more distal and more proximal (carotid siphon, extracranial carotid artery) pathology. Patients with only distal M2 or only M3 occlusions were excluded because visual assessment of collaterals in a small arterial territory was considered insufficiently reliable.

Clinical variables

Demographic data (age and gender), medical history and vascular risk factors (such as previous cerebrovascular events, arterial hypertension, diabetes mellitus, dyslipidemia, smoking, and atrial fibrillation) were recorded. We collected pre-stroke modified Rankin scale (mRs) and current medications at the time of stroke. We recorded "new neurological deficits", that are new (i.e. not preexisting), focal neurological deficits, such as visual field defects, eye deviation, aphasia, neglect and vigilance impairment, assessed by a neurologist during the initial evaluation of a patient with suspected acute ischemic stroke, as noted in the medical records. Stroke severity was scored by National Institutes of Health Stroke Scale (NIHSS). We measured vital signs (body temperature, and blood pressure), metabolic and hematologic parameters at admission and calculated onset-to-door, onset-to brain imaging and onset-to treatment times. Stroke etiology was classified according to the TOAST classification, with dissection and multiple causes added as categories. Clinical outcome was measured at 3 months with the mRs either in person at the outpatient stroke clinic, or by standardized telephone interview by Rankin-certified medical personnel. Favorable outcome was considered as 3 months mRs ≤ 2.

Imaging protocol and analysis

We assess all individuals with suspected AIS by a multimodal CT scan as part of their standard of care, unless contrast contraindication exists. Non-contrast CT (NCCT) scanning was performed to detect intracranial haemorrhage, hyperdense MCA sign and chronic cerebrovascular lesions (defined as presence of chronic infarct and/or leukoaraiosis ≥ 1 according to Blennow scale). Early ischemic changes in the MCA territory were recorded to calculate ASPECTS.

CTA in helical mode was performed from the aortic arch to the top of the frontal sinuses (120 KV, 150–260 mAs, 0.625 slice-thickness, 50 ml of iodinated contrast at 5 ml/s, delay according to the perfusion data). On CTA, we searched for significant extracranial carotid pathology in the ischemic territory, defined as the presence of ≥ 50% stenosis, occlusion, dissection or floating thrombus. Significant intracranial pathology, i.e. ≥ 50% stenosis or occlusion, was grouped as proximal if it involved carotid siphon, proximal M1 (i.e. less than 10 mm from M1 origin) or A1 segment, and distal if it involved distal M1, M2, M3 or A2 segment. We calculated clot burden score (CBS) as indicator of clot extension. The collateral score was visually determined from CTA maximal intensity projection

reconstructions and graded according to Tan et al. [11] Absence of collateral flow to the ischemic territory was graded as 0, whereas collateral flow in ≤ 50%, > 50% and ≥ 100% of the vessels filling in the ischemic territory distal to the occluded artery was graded as 1 (poor collaterals), 2 (moderate collaterals), and 3 (good collaterals), respectively. Interrater agreement for collateral grading 0–1 vs. 2–3 was evaluated on 100 consecutive patient's proximal intracranial occlusions using Cohen's kappa.

Statistical analysis

We first performed a univariate analysis (UVA) between demographic, clinical, metabolic and radiological variables depending on collateral status. All grades of collaterals, considered as ordinal categorical variable (0–3), were considered for the primary outcome of the study.

All variables from the UVA, independently from their statistical significance in univariate comparisons, were then used to fit three multivariate logistic models to determine the independent associations with better degrees of collateralization. First, we performed a clinical multivariate analysis (MVA-A) using only demographic, clinical and laboratory variables available before the acquisition of CTA, to provide clinicians with indicators of patients likely to have good collaterals. Second, we analyzed the radiological variables that are independently associated with better collaterals (MVA-B), to provide radiologists with additional information about NCCT variables capable to predict good collaterals. Third, we combined the variables from the two above mentioned models and used all demographic, clinical, metabolic and radiological variables in a comprehensive MVA (MVA-C). This comprehensive analysis aimed to show the most powerful (clinical or radiological) associations, and better understand the pathophysiology of good collaterals.

All analyses were performed using the proportional odds approach. In all MVA analyses, imputation of missing values was carried out using multiple chain equations methodology [12]. In this way, we generated five complete datasets. Analysis of each dataset was performed separately. We used backward elimination techniques to report only covariates significantly associated with the outcome, listed in Table 2. The reported results were obtained by appropriately combining the results of the five imputed analyses. In all analyses, type I errors of 5% to test each regression coefficients separately were used. The R package (R version 3.4.1) was used throughout.

Given that the 3 months clinical outcome was considered a secondary, ancillary result, no adjustment was done for this analysis.

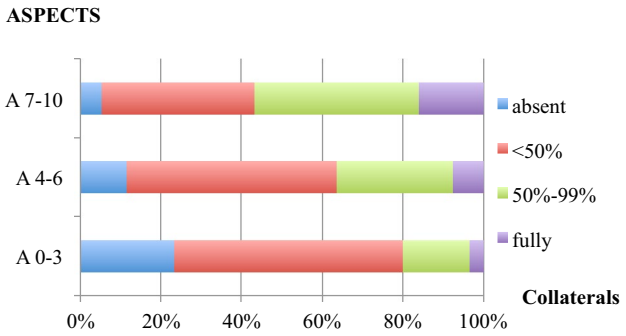

Fig. 1 Correlation between ASPECTS score and collaterals (ordinal)

Results

Among 2027 patients with AIS involving MCA territory and with good quality acute CTA during the study period, 857 met the inclusion criteria (Suppl. Fig. 1S). Median age was 72.3 (interquartile range, IQR 20.5) years, 415 (48.4%) were females and median admission NIHSS was 16 (IQR 9). Median onset to CT time was 2.5 (IQR 3.4) h. CTA showed M1 occlusion in 620 (72.3%) and proximal M2 occlusion in 237 (27.7%) patients. Collaterals were graded as absent (grade 0) in 77 (9.0%), poor (grade 1) in 345 (40.3%), moderate (grade 2) in 307 (35.8%) and good (grade 3) in 128 (14.9%) patients. Interrater agreement for collateral grading 0–1 vs. 2–3 was 0.81.

Table 1 shows patient characteristics, laboratory and radiological findings of the study population as well as the results of the univariate analysis (Suppl. Tables 1S and 2S, are extended versions of Table 1). The distribution of vascular risk factors was similar among the collateral scores.

Significant results from the MVAs are shown in Table 2. In the clinical MVA (MVA-A), better collaterals were associated with lower age (OR 0.99, confidence intervals: see Table 2), lower NIHSS on admission (OR 0.94, see also Suppl. Fig. 2S) and lower frequency of visual field defects (OR 0.70), eye deviation (OR 0.66) and decreased vigilance (OR 0.60). Better collaterals were also associated with non-smoking status (OR 0.72) and decreased delay to imaging (OR 0.97). When limiting the MVA to radiological variables (MVA-B), better collaterals were associated with a higher ASPECTS score (OR 1.27), higher CBS (OR 1.15), and absence of chronic cerebrovascular lesions (OR 0.72).

Combining all data in a comprehensive MVA (MVA-C), better collaterals were associated with lower age (OR 0.99), hemineglect (OR 1.35), absence of visual field defects (OR 0.64), eye deviation (OR 0.58) and decreased vigilance (OR 0.62). Better collaterals were also associated with dyslipidemia (OR 1.57), absence of statin use (OR 0.96) and lower creatinine levels (OR 0.99). Moreover, we confirmed the positive association between better

Table 1 Patient characteristics, laboratory and radiological findings in the study population

Baseline variable and follow-up as median ± IQR or *n* (%)	Total pt (*N* = 857)	OR	95% CI
Age (years)	72.3 (20.5)	0.99*	0.98–1.00
Sex (females)	415/857 (48.4%)	1.08	0.84–1.38
Admission NIHSS	16.0 (9.0)	0.91*	0.89–0.92
New neurological deficit			
Visual field defects	619/836 (74.0%)	0.34*	0.25–0.46
Eye deviation	477/835 (57.1%)	0.35*	0.27–0.46
Aphasia	435/842 (51.7%)	1.04	0.81–1.33
Neglect	431/835 (51.6%)	0.89	0.69–1.14
Vigilance impairment	163/836 (19.5%)	0.34*	0.25–0.48
Premorbid risk factors			
Hypertension	537/852 (63.0%)	0.88	0.68–1.14
Diabetes	134/852 (15.7%)	0.85	0.61–1.19
Hyperlipidemia	581/851 (68.3%)	1.20	0.92–1.57
Current smoking	206/841 (24.5%)	0.87	0.65–1.17
Atrial fibrillation	351/854 (41.1%)	0.78	0.61–1.01
Pre-stroke mRS > 2	68/850 (8.0%)	0.89	0.57–1.40
Statin use before stroke	215/846 (25.4%)	0.75	0.57–1.00
Laboratory studies			
Blood glucose (mmol/L)	6.7 (2.0)	0.93*	0.88–0.98
Serum creatinine (mg/dL)	87.0 (29.0)	0.99*	0.99–1.00
Total cholesterol (mmol/L)	5.1 (1.6)	1.01	0.99–1.03
Onset to CT time (h)	2.5 (3.4)	0.98	0.95–1.01
Neuroimaging data			
ASPECTS score	8.0 (4.0)	1.32*	1.25–1.39
Significant leukoaraiosis	212/857 (24.7%)	0.84	0.63–1.11
Hyperdense MCA sign	398/857 (46.4%)	0.54*	0.42–0.70
Clot burden score	6.0 (4.0)	1.22*	1.16–1.27
Significant extracranial carotid pathology			
Significant stenosis	69/856 (8.1%)	0.73	0.46–1.16
Any occlusion	184/856 (21.5%)	0.59*	0.43–0.81
TOAST mechanism[†]			
Atherosclerosis	114/828 (13.8%)	0.81	0.56–1.19
Cardiac	396/828 (47.8%)		
mRS at 3 months			
0–2	308/760 (40.5%)	0.35*	0.26–0.46

Odds ratios (OR) with confidence intervals (95% CI) from the univariate analysis of better vs. poorer collaterals are given, with collaterals used as an ordinal variable quantified by four grades

*Asterisks denote significant findings

[†]Reference: atherosclerosis

collaterals and higher ASPECTS (OR 1.27 and Fig. 1) and higher CBS (OR 1.09 and Fig. 2), respectively.

As an ancillary result, we found in unadjusted analysis that a better collateral status was associated with favorable clinical outcome at 3 months (Table 1).

Discussion

In this largest retrospective study of collaterals so far, we investigated factors that are associated to their variability

Table 2 Results of the pre-imaging multivariate analysis (MVA-A), the imaging-only MVA (MVA-B), and the comprehensive MVAs (MVA-C)

	OR	95% CI	*p* value
MVA-A (clinical variable)			
Age	0.99	0.98–1.00	<0.01
Admission NIHSS	0.94	0.92–0.97	<0.01
Visual field defects	0.70	0.49–1.00	0.04
Eye deviation	0.66	0.48–0.91	0.01
Vigilance impairement	0.60	0.41–0.86	<0.01
Current smoking	0.72	0.53–0.98	0.04
Onset to CT time (h)	0.97	0.94–1.00	0.03
MVA-B (radiological variable)			
ASPECTS score	1.27	1.20–1.34	<0.01
Clot burden score	1.15	1.09–1.20	<0.01
Chronic cerebrovascular lesions	0.72	0.54–0.96	0.03
MVA-C (variable)			
Age	0.99	0.98–1.00	<0.01
Visual field defects	0.64	0.46–0.90	<0.01
Eye deviation	0.58	0.43–0.79	<0.01
Neglect	1.35	1.03–1.76	0.03
Vigilance impairment	0.62	0.44–0.88	<0.01
Statin use	0.69	0.50–0.95	0.02
Hyperlipidemia	1.57	1.16–2.13	<0.01
Serum creatinine	0.99	0.99–1.00	<0.01
ASPECTS score	1.27	1.20–1.35	<0.01
Clot burden score	1.09	1.03–1.14	<0.01

Only significant associations are shown

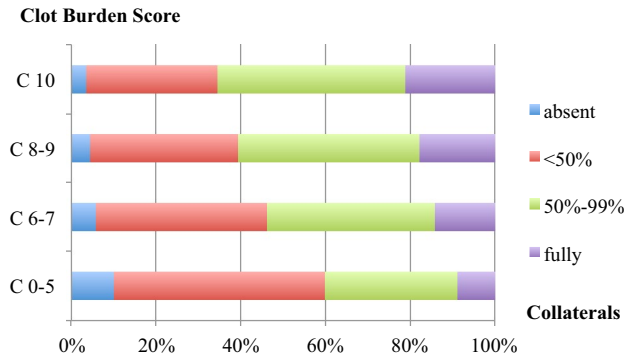

Fig. 2 Correlation between Clot Burden Score and collaterals (ordinal)

in patients with AIS and proximal MCA occlusion. We found that favorable collateral patterns could be predicted by lower age, non-smoking status, no previous statin use, dyslipidemia and lower serum creatinine. Better collaterals were more frequently observed in patients with shorter delay to imaging and absence of chronic cerebrovascular lesions. Moreover, better collaterals were associated with lower stroke severity, lower frequency of cortical signs (except for hemineglect), higher ASPECTS and lower clot burden.

The association between younger age and better collateral score is in agreement with previous findings [8, 9]. It has been proposed that aging leads to 'collateral rarefaction', a process causing reduction in collateral density and diameter, probably mediated by prolonged endothelial dysfunction [13]. Among vascular risk factors, current smoking was an independent predictor of poorer collaterals in our clinical analysis. The role of smoking in the impairment of collateral extent in the coronary and peripheral bed is well known [14], but studies examining its association with leptomeningeal collateral status in humans are lacking. To the best of our knowledge, there have been no previous reports noting that renal impairment was associated with poor cerebral collaterals. However, hyperuricemia, known to be related to chronic kidney disease, and the presence of metabolic syndrome, have recently been associated with worse collaterals [8]. These findings allow us to generate hypotheses with regard to underlying pathophysiology of collateral formation. Aging, smoking and impaired renal function could reduce collateral extent by either causing endothelial dysfunction or decreasing dilatatory capacity of the pial arteries [15].

Somewhat unexpectedly, known or newly diagnosed dyslipidemia was associated with better and statin use with poorer collaterals. Previous reports on coronary artery disease demonstrated a positive association of hypercholesterolemia and collateral extension, probably mediated by elevated levels of vascular endothelial growth factor [16]. Regarding statin use, our findings may be viewed as contradictory and not consistent with previous studies suggesting a role for statins in the promotion of arteriogenesis [6, 17]. In our study, it seems that untreated (newly diagnosed) hyperlipidemia may be a major promoter of collaterogenesis, rather than known and treated hyperlipidemia (i.e. statine use).

A shorter delay from symptoms onset to baseline imaging was independently associated with better collaterals, supporting the concept of time-dependent 'collateral-failure' [18, 19]. In the purely radiological analysis, absence chronic infarcts and leukoaraiosis were associated with better collaterals. Leukoaraiosis might be associated with increased arterial stiffness, which lead to less recruitment of collaterals in the acute phase of occlusive ischemic stroke [20].

In our study, lower rate of cortical signs (i.e. eye deviation and visual field defects) were associated with better collaterals. This is consistent with the anatomical observation that leptomeningeal collaterals mainly supply cortical peripheral areas, whereas deeper structures are predominantly supplied by perforating arteries [21]. Only hemineglect did not fit this pattern, possibly indicating that the critical site of temporal damage responsible for hemineglect is mostly

supplied by non-anastomosing arterial systems [22]. The positive association with higher ASPECTS suggests that a higher degree of collaterals may prevent infarct growth [19]. Moreover, higher clot burden may obstruct more orifices of arteries that could provide collateral blood flow. Inversely, one could hypothesize that collaterals may influence clot length, because patients with poor collaterals may have an increased degree of stasis around the clot and this could lead to a clot extension [23].

The association of collateral status with clinical outcome was not a main goal of our study. Still, the fact that patients with good collaterals showed a better outcome in unadjusted analysis stresses the need to adjust for this variable when reporting outcomes after revascularization treatments.

The limitations of our study include its retrospective design and its single center nature. In addition, collaterals were estimated semi-quantitatively and CTA-based collateral assessment may be less precise than invasive contrast angiography. Moreover, the use of single-phase CTA may lead to technique-dependency bias in collaterals evaluation due to variability in the timing of the contrast injection and image acquisition.

Conclusions

Our study showed that younger age, non-smoking status, dyslipidemia and lower serum creatinine were predictors of better collaterals in patients with AIS and proximal MCA occlusion. The implications of our findings are several: first, they may add to our understanding of collaterals variability at baseline, indicating that risk factors for diffuse vascular pathology (i.e. smoking, aging, renal function impairment) may play a detrimental role in the development and recruitment of such anastomoses. Conversely, dyslipidemia may exhibit a promoting effect upon angiogenesis. Second, our data suggest that manipulation of physiological parameters such as blood pressure or sugar may not result in better collateral flow, but the latter seems to be largely determined by non-modifiable factors in the acute phase of stroke. Third, the associations between collateral status and ASPECTS, clot burden, and frequent cortical signs suggest that these elements are related and partly interchangeable, measuring similar aspects of the ischemic pathophysiology. These characteristics could be used to identify patients with better collaterals for more aggressive revascularization treatment, even at later timepoints.

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Author contributions SN studied the concept and design, helped in analysis and interpretation, and preparation of the article. GS, CWC and DS helped in interpretation of data and critical revision of the article for important intellectual content. DL carried out data analysis and interpretation and helped in preparation of the article. AE helped in data acquisition and analysis. PJM helped in radiological data acquisition and critical revision of the article for important intellectual content. MW contributed to the conception and design, and helped in the interpretation of radiological data. PM studied the concept and design, and helped in data acquisition, analysis and interpretation, critical revision of the article for important intellectual content, study supervision.

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Compliance with ethical standards

Conflicts of interest In the last 3 years, Prof. P. Michel received research grants from the Swiss Heart Foundation, Boehringer Ingelheim and BMS through his institution; speaker fees from Boehringer Ingelheim, Bayer, Daiichi Sankyo, Medtronic and Amgen; honoraria from scientific advisory boards from Boehringer Ingelheim, Bayer, Pfizer and BMS and consulting fees from Medtronic, Astra-Zeneca and Amgen. His institution (CHUV), receives all of the support for stroke education and research. Dr. G. Sirimarco served on scientific advisory boards for Amgen and Daiichi Sankyo. Dr. C.W. Cereda received research grants from the Swiss Heart Foundation, Advisory Board of Research (EOC) and Boehringer Ingelheim in the last 3 years through his institution; honoraria from scientific advisory boards from Boehringer Ingelheim, Bayer and Pfizer. The other authors report no conflicts of interest.

Ethical standards Collection, analysis and publication of data in ASTRAL was approved by the institution's ethical commission.

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