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Acute Bihemispheric Stroke from a Single Carotid Source: Risk Factors, Mechanisms and Outcome

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Abstract

Background— Mechanisms and natural history of acute bihemispheric strokes (ABSs) from a single carotid source are little known. Aim of our study was to identify risk factors, mechanisms and outcome in ABS from a single carotid source in a consecutive series of ABS patients.

Methods— From the ASTRAL registry (2003-2018) we retrospectively selected patients with acute ischemic lesion(s) in one or both carotid territories confirmed on brain DWI-MRI, significant carotid artery disease (>50% stenosis or acute dissection) in the arterial territory(ies) involved, and no other concomitant stroke etiology. Baseline features and outcome of patients with ABS were compared to all patients with unilateral ischemic lesions and to a group matched for age, grade of stenosis and etiology of the carotid disease (atherosclerosis or dissection).

Results— We included 184 patients having median age of 65.3 years (IQR 53.5-77.1) and median NIHSS of 6. Twenty-three patients (12.5%) had ABS, while 161 had unilateral lesions. In the multivariate analysis of the matched cohort, patients with ABS had significantly lower diastolic blood pressure (DBP) on admission (OR 0.96; 95%CI 0.92-1.00, p=0.04), more frequently contralateral internal carotid (ICA) occlusion (OR 49.79; 95% CI 2.99-829.82, p=0.01) and absence of anterior communicating artery (ACoA) (OR 14.28; 95%CI 3.03-100, p=0.00). ABS was associated with lower probability of 3-month functional independence (adjOR 0.24; 95%CI 0.06-0.92, p=0.04).

Conclusions— Bihemispheric stroke may occur in stroke patients with a single carotid source. Their association with lower admission DPB, contralateral ICA occlusion and absence of ACoA suggests contralateral hypoperfusion as the main mechanism.

Keywords— Acute bihemispheric stroke, carotid stenosis, Willis circle patency, stroke mechanism.

INTRODUCTION

Acute bihemispheric stroke (ABS) from unilateral carotid artery disease and in the absence of a cardioembolic source are infrequent,[1] however the growing use of MRI is leading to increased recognition of this condition, which may account for up to 6% of all carotid strokes.[1,2,3] Multiple arterial territory lesions are usually attributed to cardiac or aortic sources,[4,5] with consequences on stroke work-up and secondary prevention.[6,7] Similarly, underestimating the pathogenic role of a carotid stenosis because of bilateral parenchymal lesions may lead to withholding revascularization therapies, highly effective in secondary stroke prevention.[8,9] Therefore, better knowledge of clinical, radiological and pathophysiological characteristics of patients with bihemispheric stroke from a single carotid source should improve clinical management and long-term outcome.

METHODS

Patient selection

The study was conducted on the Acute STroke Registry and Analysis of Lausanne (ASTRAL) that collects all consecutive acute ischemic strokes (AIS) admitted to the stroke unit and/or intensive care unit of Lausanne University Hospital (CHUV), presenting within 24 hours of stroke onset or last

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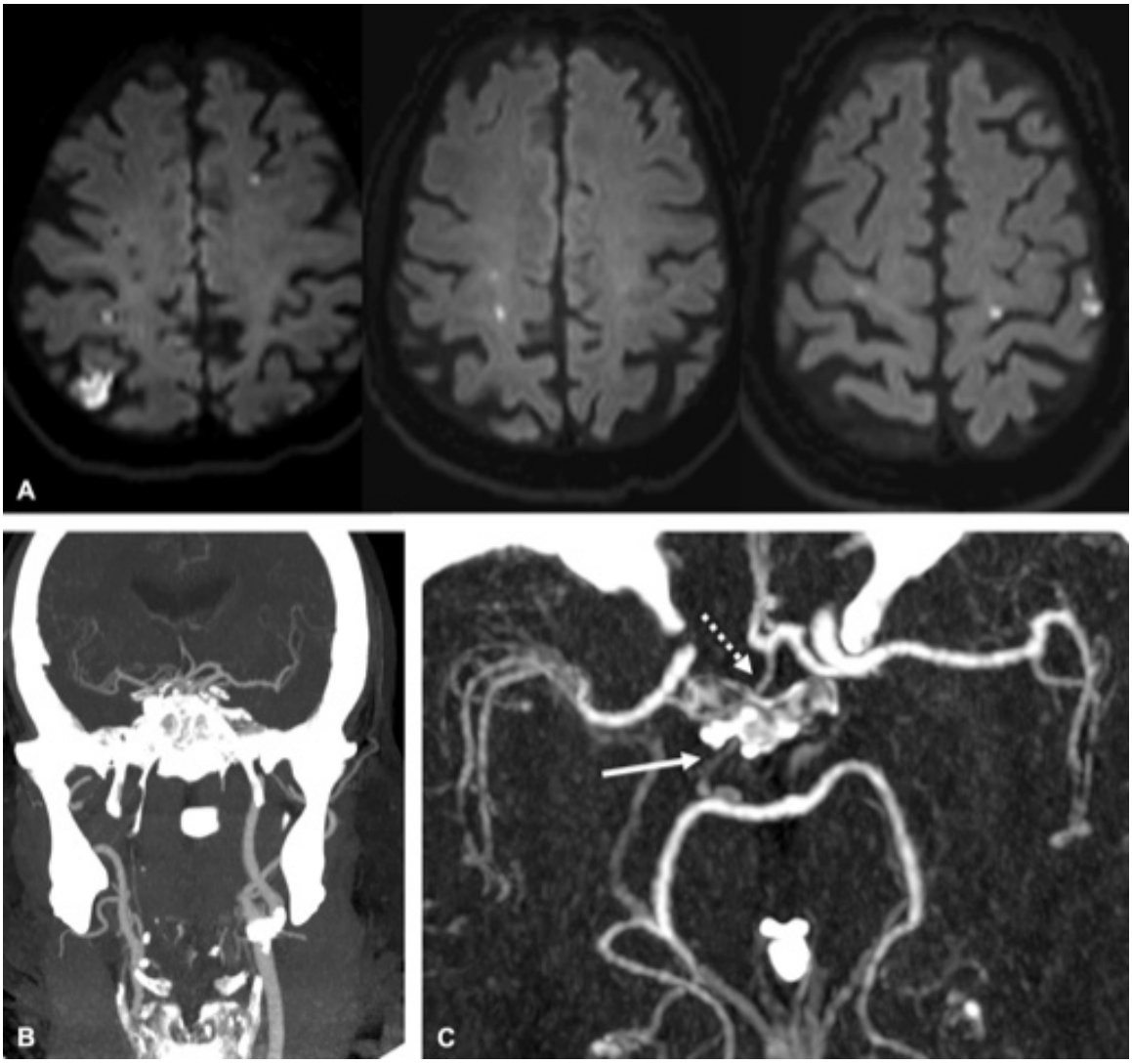

FIGURE 1: Example of a patient with acute bihemispheric strokes. He presented to the emergency room of our hospital for acute onset of right facial palsy and right arm paresis. A: acute brain MRI with DWI shows acute ischemic lesions in both MCA territories and in the boarderzone between ACA and MCA territories. Subacute CT angiography shows B: chronic occlusion at the origin of right ICA and severe atherosclerotic stenosis at the origin of left ICA and C: incomplete Willis circle with small right A1 segment (dashed arrow), small right PCoA (continuous arrow) and absent left PCoA.

proof of good health.[10] Stroke etiology are estabilished according to TOAST classification.[11]

From all consecutive patients entered in ASTRAL between 1/2003 and 11/2018, we selected cases applying the following inclusion criteria: 1) acute ischemic lesion(s) in one or both anterior circulation territories demonstrated on DWI sequence and no lesion in the vertebrobasilar territory 2) good quality vascular imaging (CTA or MRA) performed within 24 hours of stroke onset (or last proof of good health) and available acute or subacute brain MRI (performed up to 9 days after stroke onset) 3) atherosclerotic plaque with ≥50% stenosis or acute dissection in the extracranial or intracranial portion of the internal carotid artery proximal to the vascular territory involved in the ischemic lesion. 4) absence of concomitant high risk cardioembolic source after adequate diagnostic work-up (see below).

In addition, we excluded patients with multiple potential stroke etiologies, and those with potential acute bilateral carotid disease, such as bilateral acute carotid dissections. We retained patients with significant contralateral atherosclerosis, since we considered a simultaneous embolization from the contralateral carotid stenosis very unlikely, and patients with contralateral carotid occlusion, regarding this latter as chronic. All patients in the study underwent transthoracic echocardiography (TEE) and rhythmic surveillance to exclude AF including 24-hours ECG monitoring in stroke unit and at least 24-hour ECG ambulatory recording (Holter). When indicated by medical history, TEE findings or in case of high suspicion of cardioembolic source, transesophageal echography was also performed to rule out valvulopathy or aortic valve disease.

From the study population we identified patients with acute bihemispheric carotid territory strokes and those with unilateral lesions. In the group of patients with unilateral lesions, we selected a subgroup of patients matching them with ABS patients for age, grade of stenosis and stroke mechanism (match: 1 ABS: 3 unilateral, see statistical analysis for details).

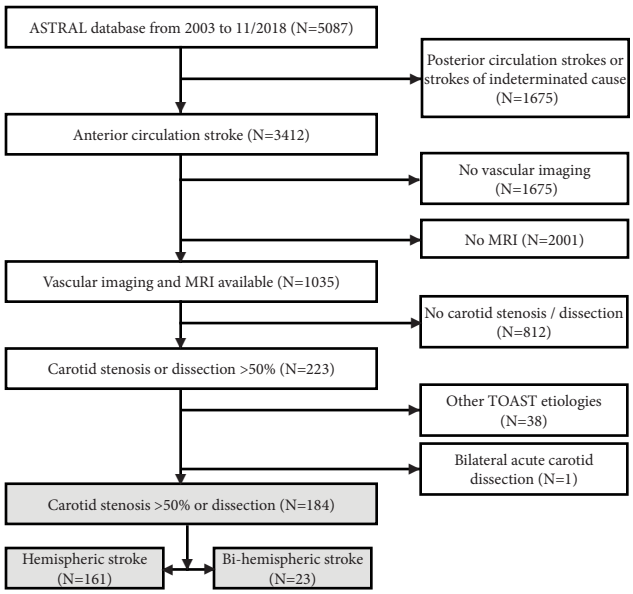

FIGURE 2: Flowchart of patient inclusion and exclusion from the study.

Variable definition and collection

ASTRAL incorporates a large range of pre-specified parameters including demographics (age and gender), medical history and cardiovascular risk factors, current medications, clinical symptoms and neurological signs and pre-hospital and door-to-treatment times. In addition, we collected: stroke localization, stroke severity at admission and 24 hours, vital signs (body temperature, blood pressure, heart rate), metabolic and hematologic parameters, acute and subacute multimodal brain imaging, acute recanalization treatment performed and their characteristics, stroke mechanism and long-term clinical outcome. We also recorded the distribution of the ischemic lesion according to anatomic structures, vascular territories and side.

Radiological variables

All selected patients underwent acute or subacute cerebral MR imaging (T1 and T2-weighted sequences, FLAIR, DWI) and MRA (TOF; intra- and extracranial MRA after gadolinium injection, if renal function permitted) (See Supplementary Methods).

The images of all included patients were reviewed by at least two experienced vascular neurologists (PS, DS, SN, GS and PM) and one neuroradiologist (VD) for acute lesions in the carotid territories.[12] An ischemic lesion was considered acute based on the well-described combinations of signal alterations on DWI, ADC and T2WI.[13] We defined acute bihemispheric strokes (i.e. ABS) the presence of synchronus acute ischemic lesions in both internal carotid artery territories on the first MRI after the index stroke. In the case of ABS, we considered the hemisphere responsible for the main stroke symptoms and with the majority of radiological lesions as the "symptomatic side". An example of patient with ABS is shown in Figure 1.

To determine the presence, severity and nature of the carotid disease, we used MRA, CTA and/or digital subtraction angiography (DSA). In cases of acute recanalization attempt, appearance of the carotid on DSA during and after the attempt were also considered. We reviewed all arterial-imaging methods used in a single patient for the final assessment of the carotid arteries.

Dissection was diagnosed in presence of a long tapered arterial stenosis, flame-shaped occlusion, double lumen, intimal flap, focal fusiform or blister-like dilatation on MRA, or intramural hematoma, i.e. a hyperintense signal on fat-saturated T1-weighted sequence on MRI.[14,15] In the case of carotid occlusion proximal to the ischemic stroke, the occlusion was assumed acute and its nature again determined by reviewing all available imaging.

Patency of the circle of Willis

In all patients with ABS and in the 1:3-matched control group, we reviewed CTA (or MRA-TOF if CTA not available) sequences to assess the patency of all segments of the Willis circle, namely the anterior cerebral artery, anterior communicating artery (ACoA), posterior cerebral artery and posterior communicating cerebral artery (PCoA). Each segment was defined as present or absent. Overall Willis patency was dichotomized as "complete" if there was a combination of complete anterior and posterior Willis circle patterns according to Krabbe-Hertkamp[16] and van Seeters' classifications,[17] and "incomplete" if at least the anterior or posterior portion of the Willis circle was incomplete. Patients with bilateral foetal type posterior cerebral artery with absence of both pre-communicating segements of the PCA were included since they were considered affcted by carotid artery stroke and not related to posterior circulation pathology.[16]

Acute stroke treatments

Acute recanalization treatment (intravenous thrombolysis [IVT] and/or endovascular treatment) and all acute stroke management and secondary prevention was performed according to written hospital guidelines (based on national,[18] American[19] and European guidelines[20]) at the time of admission.

Similarly, the decision to perform subacute carotid revascularization was according to written multidisciplinary hospital guidelines[21] that mirror Swiss and European[9] recommendations.

Outcomes

Rankin score was assessed by Rankin-certified personnel at 3 and 12 months in the outpatient clinic using the modified Rankin score (mRS). Outcome is assessed by a delta-mRS (the difference between the 3-month (12-month) mRS and the prestroke mRS). Outcome was considered favorable if the difference between long-term and prestroke mRS was ≤ 2 for the corrected mRS. The time to the first recurrent stroke or TIA was recorded for the first 12 months.

Statistical analysis

We summarized continuous data as median values with interquartile range (IQR) and categorical data as absolute numbers with percentages. Univariate group comparison was

TABLE 1: Baseline demographics, clinical and radiological characterization of the whole cohort, acute bihemispheric stroke and unmatched patients with unilateral lesions. For numerical are displayed median and interquartile range. P-value of Fisher's exact test for categorical data and Mann-Whitney U tests for numeric variables. mRS= modified Rankin score; NIHSS= National Institute Health Stroke Scale; VA = Vertebral artery.

Variable	Total (n=184)	Bilateral strokes (n=23)	Unilateral stroke (n=161)	P-value
Age	65.3 (53.5-77.1)	70.3 (59-83.7)	63.9 (53-76.4)	**0.04**
Female sex	63 (34.2%)	7 (30.4%)	56 (34.8%)	0.82
Hypertension	116 (63%)	20 (87%)	96 (59.6%)	**0.01**
Diabetes	26 (14.1%)	5 (21.7%)	21 (13%)	0.33
Hypercholesterolemia	143 (77.7%)	18 (78.3%)	125 (77.6%)	1.00
Smoking	65 (35.3%)	9 (39.1%)	56 (34.8%)	0.82
Coronary artery disease	20 (10.9%)	4 (17.4%)	16 (9.9%)	0.29
Prosthetic valves	1 (0.5%)	1 (4.3%)	0 (0%)	0.16
Active cancer	12 (6.5%)	3 (13%)	9 (5.6%)	0.18
mRS pre-stroke (0-2)	176 (95.7%)	18 (78.3%)	158 (98.1%)	**0.00**
Previous stroke or TIA or amaurosis	29 (15.8%)	5 (21.7%)	24 (14.9%)	0.37
Antiplatelets at stroke onset	57 (31%)	7 (30.4%)	50 (31.1%)	1.00
Anticoagulants at stroke onset	4 (2.2%)	1 (4.3%)	3 (1.9%)	0.42
Antihypertensives	87 (47.3%)	13 (56.5%)	74 (46%)	0.38
Statins	44 (24%)	4 (18.2%)	40 (24.8%)	0.60
Baseline NIHSS	6 (3-13)	4 (2.3-9.8)	6 (3-13)	0.59
Acute systolic blood pressure (mmHg)	147.5 (131.4-160.6)	148 (130.2-162.7)	147 (140-158)	0.82
Acute diastolic blood pressure (mmHg)	82 (71.4-90)	75 (65.3-80)	84 (72.2-91.7)	**0.02**
Stroke mechanism				0.09
Atherosclerotic	130 (70.6%)	20 (87%)	110 (68.3%)	
Dissection	54 (29.4%)	3 (13%)	51 (31.7%)	
Chronic ischemic lesion on imaging	53 (28.8%)	7 (30.4%)	46 (28.6%)	0.81
Leukoaraiosis	56 (30.4%)	11 (47.8%)	45 (27.9%)	0.09
Site of symptomatic carotid artery lesion				
Intracranial	4 (2.7%)	0 (0%)	4 (2.5%)	1.00
Extracranial	180 (97.3%)	23 (100%)	157 (97.5%)	
Degree of symptomatic carotid artery lesion				**0.04**
Stenosis less 50%*	8 (4.3%)	0 (0%)	8 (5%)	
Stenosis 50-99%	98 (53.3%)	18 (78.3%)	80 (49.7%)	
Occlusion	78 (42.4%)	5 (21.7%)	73 (45.3%)	
Degree of asymptomatic carotid artery lesion				**0.00**
Stenosis less 50%	141 (76.5%)	12 (52.2%)	128 (80%)	
Stenosis 50-99%	35 (19.1%)	7 (30.4%)	28 (17.5%)	
Occlusion	8 (4.4%)	4 (17.4%)	4 (2.5%)	
Extracranial VA stenosis	11 (6.9%)	4 (23.5%)	7 (4.9%)	**0.02**
Extracranial VA occlusion	9 (5.9%)	0 (0%)	9 (6.6%)	0.60
Acute treatment				0.56
Conservative treatment	107 (58.1%)	12 (52.2%)	95 (59%)	
IV thrombolysis	46 (25%)	5 (21.7%)	41 (25.5%)	
Bridging	24 (13%)	5 (21.7%)	19 (11.8%)	
Direct mechanical thrombectomy	6 (3.3%)	1 (4.3%)	5 (3.1%)	
Thrombectomy attempted, but already recanalized	1 (0.5%)	0	1 (0.6%)	
3-month mRS 0-2	121 (66.8%)	10 (43.5%)	111 (70.2%)	**0.02**
12-month mRS 0-2	127 (70.6%)	11 (47.8%)	116 (73.9%)	**0.02**
3-month mortality	7 (3.9%)	3 (13%)	4 (2.5%)	**0.05**
12-month mortality	14 (7.8%)	5 (21.7%)	9 (5.7%)	**0.02**
1-year stroke recurrence	15 (9%)	4 (19.1%)	11 (7.5%)	0.10

* In all patient with stenosis <50% the underlying lesion was an arterial dissection

TABLE 2: Comparison of Willis circle characteristics between unilateral and bihemispheric ischemic stroke patients. Abbreviations: A1: anterior cerebral artery first segment; P1: posterior cerebral artery first segment; PCoA: posterior communicating cerebral artery.

Variable	Total (n=92)	Bilateral strokes (n=23)	Unilateral stroke (n=69)	P-value
Overall complete Willis patency	19 (20.6%)	2 (8.7%)	17 (24.6%)	**0.14**
Ipsilateral A1 present	90 (97.8%)	23 (100%)	67 (97.1%)	1.00
Contralateral A1 present	85 (92.4%)	19 (82.6%)	66 (95.7%)	**0.06**
Absence anterior communicating artery	35 (38%)	16 (69.6%)	19 (27.5%)	0.00
P1 and PCoA present	19 (20.6%)	2 (8.7%)	17 (24.6%)	0.14

performed using Fisher's exact test for categorical variables and Mann–Whitney U test for continuous variables. First, we compared baseline variables and short-term outcomes between ABS and unilateral lesion groups.

Then, using a 1:3 exact-matching procedure, for each patient with ABS we randomly selected three patients with an similar degree of carotid stenosis (categorized as <50%, 50-99% and occlusion), stroke mechanism and lesion site (intracranial or extracranial) from the unilateral-lesion group.

We performed a multivariate logistic regression analysis in the matched cohort to identify variables independently associated with ABS. For this, all variables associated with ABS in the univariate analysis at a significance level $p<0.1$ were entered into the model and then stepwise procedure was used to select the statistically significant covariates. To test for collinearity between the covariates of the multivariate model, we calculated the adjusted generalized variance-inflation factor (VIF) for each covariate.

To better characterize the relationship of ABS with 3-month functional outcome and 1-year stroke recurrence, we performed a multivariate logistic regression analysis of the whole cohort adjusted for potential confounders, such as age, baseline NIHSS and pre-stroke mRS.

We performed statistical analysis with R statistical software (version 3.3.2, R Core Team [2016], R Foundation for Statistical Computing, Vienna, Austria). P-values <0.05 were considered significant. As the analysis was exploratory, no correction for multiple analyses was applied.

This observational study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[22]

Data availability statement

Anonymized participant data are available upon reasonable request that should include a data analysis and publication plan.

RESULTS

After applying the inclusion and exclusion criteria of the study, 184 patients were included with a median age of 65.3 years (IQR 53.5-77.1), 34% of females and a median NIHSS of 6 points (IQR 3-13). The numbers of the excluded patients and reasons for exclusion are detailed in Figure 2. Among the 184 patients included, 23 (12.5%) had ABS and 161 patients unilateral stroke. Half of patients with ABS (12/23) had non-significant pathology (<50% stenosis) in the contralateral/asyptomatic carotid artery.

Among the 23 patients with bilateral stroke, the ischemic lesions found in the contralateral hemisphere were border-zone infarcts in 13 patients (57%), embolic in five (21%) and mixed in five (22%). All these lesions were asymptomatic. No patient presented an azygos anterior cerebral artery confiuguration.

The univariate analysis of the whole cohort showed that ABS patients were older; more frequently affected by hypertension and had lower admission diastolic blood pressure (DPB). Degree of stenosis in the symptomatic carotid artery was lower in ABS patients, as shown in Table 1. Compared to patients with unilateral lesions, ABS patients more frequently had a significant extracranial carotid disease on the asymptomatic side (stenosis >50% 30.4% vs. 17.5%, occlusion 17.4% vs. 2.5%, $p<0.01$) and in the vertebral arteries (23.5% vs 4.9%, $p=0.02$). We found the same differences in the univariate analysis on the 1:3-matched cohort (Supplementary-Table I). In addition, ABS patients more frequently had absence of ACoA (Table 2). In the multivariate analysis of the matched cohort, lower admission DPB, contralateral ICA occlusion and absence of ACoA remained independent predictors of ABS (Table 3).

The proportion of functionally independent patients (mRS 0-2) at 3 and 12 months was lower in ABS patients in the univariate analysis in both unmatched (Table 1) and matched (Supplementary-Table I) cohorts. This association remained significant in the multivariate analysis at 3 months in the whole cohort (adjOR, 0.28; 95%CI 0.09-0.87, Supplemen-

TABLE 3: Multivariate logistic regression analysis for bilateral ischemic lesions (vs. unilateral) in the matched cohort. DPB= Diastolic blood pressure; ICA= internal carotid artery.

	Matched cohort	
Variable	**OR (95%CI)**	**P-value**
Acute DBP	0.96 (0.92-1.00)	**0.04**
Contralateral ICA disease		
Contralateral ICA stenosis 50-99%	1.71 (0.36-8.13)	0.50
Contralateral ICA occlusion	49.79 (2.99-829.82)	**0.01**
Absence of anterior communicating artery	14.28 (3.03-100.00)	**0.00**

tary Table II), with a similar trend at 12 months (adjOR, 0.45; 95%CI 0.14-1.50, Supplementary Table II). In the ABS group, stroke recurrence was twice as frequent both in the whole and matched cohort of patients with unilateral lesions; this result did not reach statistical significance. We observed a similar trend, in the age-adjusted analysis of the whole cohort (adjOR, 2.77; 95%CI 0.77-9.94, Supplementary Table II).

DISCUSSION

In a large cohort of consecutive AISs assessed with brain MRI, we found ischemic lesions in both carotid territories in 12.5% of patients with unilateral acute carotid artery disease. Lower admission DPB, contralateral ICA occlusion and absence of ACoA were independently associated with ischemic lesions in both carotid territories. Bilateral ischemic lesions were associated with worse 3- and 12-month outcomes and a potentially higher risk of stroke recurrence at 12 months.

Data regarding the frequency of bilateral ischemic lesion from unilateral carotid disease are scant, due to not systematically MRI use in the acute phase of stroke care and/or include patients with ischemic lesions in the posterior circulation. However, our incidence of 12.5% of bilateral lesions seems in agreement with these studies,reporting a frequency of 11 to 15%.[3,23,24]

Previous studies did not investigate the variables associated with bilateral ischemic lesion in the case of acute carotid disease. The association we found between ABS and lower diastolic blood pressure on admission could suggest hemodynamic mechanisms underlying the bilateral lesions. Furthermore, concomitant occlusion of the contralateral carotid artery may entail a fragile balance in blood supply on both anterior circulations, which may not be adequately compensated in case of acute hemodynamic fluctuations, thus leading to bilateral lesions. In addition, absence of the ACoA hints at hemodynamic mechanisms being responsible for bilateral lesions. The three elements suggest the contralateral hypoperfusion as the main stroke mechanism rather than passage of microemboli through the ACoA as hypothesized previously.[23] This is further supported by our finding of a high frequency of border zone infarcts (57%, n=12/23) in the hemisphere contralateral to the carotid lesion. A similar prevalence was found in another study where 5 patients out 8 (62,5%) had internal border zone infarct of centrum semiovale (CSO) contralaterally to acute carotid occlusion: etiology was retained to be "flow-steal" from affected hemispher via ACoA followed by lesion in the hypoperfused contralateral CSO. Similarly, the lesions with embolic-appearance may be favored by hemodynamic mechanism, through slow washout of embolic material.[25,26,27]

Compared to patients with unilateral lesions, ABS patients had worse functional outcomes at 3 and 12 months. The higher lesion load in ABS, the reduced ability to recruit the opposite ("healthy") hemisphere to compensate for ipsilateral stroke deficits and the higher stroke recurrence rate could explain this result. Furthermore, patients with ABS had more frequently absence of ACoA segment: absence of ACoA was an indipendent predictor of worse functional outcome regardless the state of the leptomeningeal circulation, in a recent thrombectomy study.[28] Anyway, the association between incompleteness of the circle of Willis and potential risk of stroke for patients with symptomatic ICA stenosis or occlusion has been already demonstrated.[16,17]

A higher trend for stroke recurrence in patients with ABS is not surprising, given that the proposed hemodynamic explanations may predispose carotid occluded-stroke patients to high recurrence rate.[29]

The most important clinical implication include that the multifocal stroke observed in both carotid territories may not stem from a proximal embolic source, such as the heart or aorta, but entirely from single carotid source. This could obviate the aggressive search for proximal sources in stroke patients having typical findings of severe ipsilateral carotid disease, contralateral radiological lesions of hemodynamic distribution, contralateral carotid chronic occlusion and absent ACoA. It may also explain acute lesions in border zones contralateral to the main stroke lesion in patients with non-stenosing carotid plaques and negative results of an extensive cardiac work-up including prolonged rhythm monitoring.

Limitations of our study include its retrospective, observational and single center design with a limited number of patients, its predominantly elderly Caucasian population and the limited assessment of the circle of Willis by non invasive imaging rather than conventional angiography.

Strengths of our work are the systematic use of MRI imaging to identify ABS, the exclusion of patients with concomitant stroke sources and the matched control population used for comparison with ABS.

In conclusion, we detected AIS lesions in both carotid territories in 12.5% of patients studied with brain MRI. Twelve patients (6.9%) had unilateral carotid lesion. Eleven patients had bilateral carotid lesions. Lower admission DPB, contralateral ICA occlusion and absence of ACoA were independently associated with ischemic lesions in both carotid territories. Bilateral ischemic lesions were associated with worse short- and long-term outcomes and a potentially higher risk of stroke recurrence at 12 months. These results may encourage a more aggressive initial antiplatelet strategy and less aggressive blood pressure lowering in at-risk-patients. Finally, more aggressive carotid revascularization procedures in the ipsilateral or contralateral carotid could be suggested, even if the higher procedural risks in patients with bilateral carotid disease[30] requires further studies to ascertain the benefit-risk ratio.

SUPPLEMENTARY MATERIAL

Supplementary material for this article is available online.

ETHICAL APPROVAL

The presented study was approved by the local IRB: "The ethics commission for research on humans of the Canton of Vaud, approved collection, analysis, and publication of data in the ASTRAL."

DISCLOSURE

Authors have nothing to disclose.

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SUPPLEMENTAL MATERIAL

SUPPLEMENTARY METHODS

CT imaging data acquisition

Cerebral CT were performed on a 16-multidetector CT scanner (LightSpeed, GE Healthcare, Milwaukee, WI, USA) until November 2005 and on a 64-multidetector CT scanner (LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA) thereafter. NCCT, PCT, CT angiography (CTA) and post-contrast series were acquired.

NCCT and post-contrast series were acquired in axial mode from the skull base to the vertex (16cm z-axis coverage) using the following imaging parameters: 120kV peak tube voltage, 320mA tube current, slice thickness 5mm, 32cm scan field of view (SFOV), 512x512 matrix. Raw data were reconstructed in the axial plane using filtered-back-projection (FBP) from January 2003 to February 2009 and using a blend of 60% adaptive statistical iterative reconstruction (ASiR) with 40% FBP from February 2009 to June 2015.

All PCT series were acquired in axial scan mode with 80kV peak tube voltage, 240mA tube current, 32cm SFOV and 512x512 matrix. PCT were positionned at the level of the basal ganglia and the third ventricle above the orbits in order to protect the lens. Eighteen groups of 4 slices of 10mm (40mm z-axis coverage) were used until November 2005, and 18 groups of 16 slices of 5mm (80mm z-axis coverage) were used from November 2005 to June 2015. Hence, PCT series did not include posterior fossa during the first three years of the study; thereafter, PCT series usually included the upper half of the posterior fossa due to increased z- axis coverage with the 64-multidetector CT scanner. PCT imaging were acquired during 50s in a cine mode with a delay of 5-7 s after the beginning of the injection of 50ml of iodinated contrast (Accupaque 300, iohexol 300mg/ml, GE Healthcare, Glattbrugg, Switzerland) at a flow rate of 5ml per second followed by 50mL of 0.9% saline solution at the same flow rate into an antecubital vein using a power injector. PCT raw data were recontructed using FBP until February 2009 and using a blend of 40% ASiR with 60% FBP from February 2009 to June 2015. PCT data were subsequently analyzed using the Brilliance Workspace Portal® (Philips Medical Systems, Cleveland, OH, USA), based on the central volume principle using deconvolution to create parametric maps of mean transit time (MTT); cerebral blood volume (CBV) was calculated from the area under the time-enhancement curves and cerebral blood flow (CBF) was derived from the formula CBF=CBV/MTT.

CT-angiography (CTA) was acquired in helical scan mode (parameters: 120kV peak tube voltage, 150- 260mA tube current, 0.984 pitch, 0.625mm slice thickness, 50cm SFOV, 512x512 matrix) from the aortic arch to the top of the frontal sinuses after the injection of 50ml of iodinated contrast (Accupaque 300, iohexol 300 mg/mL) at a flow rate of 5ml per second (delay according to the perfusion data) followed by 50mL of 0.9% saline solution at the same flow rate. CTA raw data were reconstructed using FBP before February 2009 and using a blend of 20% ASiR with 80% FBP afterward.

CTA data acquisition

CT-angiography (CTA) in helicoidal mode was performed from the aortic arch to the top of the frontal sinuses (120 KV, 150-260 mA, 0.625 slice thickness, 50ml of iodinated contrast at 5ml/s, delay according to the perfusion data) as standard of care, except in patients with specific contraindications including creatinine clearance below 30 ml/min/1.73m2 (50 if patient was under metformin) or known contrast allergy as previously published [15].

CTA source images and maximum-intensity projections were analyzed for focal arterial stenosis ≥50% or occlusion. CTP was assessed for acute focal hypoperfusion

MRI imaging

Acute MRI was performed on a 3 Tesla scanner (Magnetom Vida®, Siemens Healthcare, Erlangen, Germany). The following sequences were acquired consecutively: sagittal gradient echo T1 (TR 400 ms, TE 2.46 ms, flip angle 70º, 3 mm slice thickness, matrix 320 x 300), axial diffusion (TR 3000 ms, TE 80 ms, 3 mm slice thickness, 52 slices, matrix 148x148, 20 directions, b-value 0 and 1000 s/mm2), axial 2D fluid attenuated inversion recovery (FLAIR, TR 9000 ms, TE 87 ms, TI 2500 ms, flip angle 150º, 3 mm slice thickness, matrix 640x480), axial gradient echo T2 (TR 1070 ms, TE 19.8 ms, flip angle 20º, 3 mm slice thickness, matrix 320 x 272), time-of-flight angiography (TR 22 ms, TE 3.6 ms, flip angle 20º, 0.5 mm slice thickness, matrix 896 x 720), cervical T1 SPACE fat sat coronal (TR 723 ms, TE 20 ms, 0.9 mm slice thickness, matrix 256 x 220), cervical MRA (TR 3.49 ms, TE 1.23 ms, TTC 5.0 sec, 0.8 mm slice thickness, matrix 448 x 336), post-contrast axial gradient echo T1 (TR 400 ms, TE 2.61 ms, 3 mm slice thickness, matrix 448 x 380) and perfusion weighted imaging (TR 1660 ms, TE 30 ms, 4 mm slice thickness, 27 slices, matrix 128 x 128, resolution time 1.5s over 90 sec). Apparent diffusion coefficient (ADC) map was also generated from diffusion weighted imaging sequence.

SUPPLEMENTARY TABLE I: Baseline demographics, clinical and radiological characterization of the matched cohort, acute bihemispheric stroke and matched patients with unilateral lesions. For numerical are displayed median and interquartile range. P-value of Fisher's exact test for categorical data and Mann-Whitney U tests for numeric variables. mRS= modified Rankin score; TIA= Transient ischemic attack; NIHSS= National Institute Health Stroke Scale; TOAST= Trial of Org 10172 in Acute Stroke Treatment; VA = Vertebral artery.

Variable	Total (n=92)	Bilateral (n=23)	Unilateral (n=69)	P-value
Age	70.5 (61.3-81)	70.3 (59-83.7)	70.6 (61.5-80.8)	0.77
Female sex	27 (29.4%)	7 (30.4%)	20 (29%)	1.00
Hypertension	70 (76.1%)	20 (87%)	50 (72.5%)	0.26
Diabetes	18 (19.6%)	5 (21.7%)	13 (18.8%)	0.77
Hypercholesterolemia	75 (81.5%)	18 (78.3%)	57 (82.6%)	0.76
Smoking	33 (35.9%)	9 (39.1%)	24 (34.8%)	0.80
Coronary artery disease	14 (15.2%)	4 (17.4%)	10 (14.5%)	0.74
Prothesic valves	1 (1.1%)	1 (4.3%)	0 (0%)	0.25
Active cancer	7 (7.6%)	3 (13%)	4 (5.8%)	0.36
Migraine	6 (6.7%)	0 (0%)	6 (9.1%)	0.33
mRS pre-stroke	0 (0-1)	0 (0-2)	0 (0-1)	0.08
Previous stroke or TIA or amaurosis fugax	19 (20.6%)	5 (21.7%)	14 (20.3%)	1.00
Antiplatelets at stroke onset	38 (41.3%)	7 (30.4%)	31 (44.9%)	0.33
Anticoagulants at stroke onset	3 (3.3%)	1 (4.3%)	2 (2.9%)	1.00
Antihypertensives	52 (56.5%)	13 (56.5%)	39 (56.5%)	1.00
Statins	27 (29.7%)	4 (18.2%)	23 (33.3%)	0.28
Baseline NIHSS	5 (3-12)	4 (2.3-9.8)	5 (3-12)	0.9
Acute systolic blood pressure (mmHg)	152 (138-166)	147 (140-158)	153 (137.4-170)	0.6
Acute diastolic blood pressure (mmHg)	82 (71.3-90)	75 (65.3-80)	86.5 (73.4-91.8)	0.012
Stroke mechanism (TOAST)	12 (13%)	3 (13%)	9 (13%)	1.00
Atherosclerotic				
Dissection				
Chronic ischemic lesion on imaging	30 (32.6%)	7 (30.4%)	23 (33.3%)	1.00
Leukoaraiosis	34 (37%)	11 (47.8%)	23 (33.3%)	0.22
Site of symptomatic carotid artery lesion				
Extracranial	92 (100%)	23 (100%)	69 (100%)	1.00
Degree of symptomatic carotid artery lesion				1.00
Stenosis 50-99%	72 (78.3%)	18 (78.3%)	54 (78.3%)	
Occlusion	20 (21.7%)	5 (21.7%)	15 (21.7%)	
Degree of asymptomatic carotid artery lesion				0.017
Stenosis less 50%	60 (65.2%)	12 (52.2%)	48 (69.6%)	
Stenosis 50-99%	27 (29.4%)	7 (30.4%)	20 (29%)	
Occlusion	5 (5.4%)	4 (17.4%)	1 (1.4%)	
Extracranial VA stenosis	7 (9.2%)	4 (23.5%)	3 (5.1%)	0.04
Extracranial VA occlusion	4 (5.6%)	0 (0%)	4 (7%)	0.57
Acute treatment				0.07
Conservative treatment	60 (65.2%)	12 (52.2%)	48 (69.6%)	
IV thrombolysis	21 (22.8%)	5 (21.7%)	16 (23.2%)	
Bridging	8 (8.7%)	5 (21.7%)	3 (4.3%)	
Direct mechanical thrombectomy	2 (2.2%)	1 (4.3%)	1 (1.4%)	
Thrombectomy attempted, already recanalized	1 (1.1%)	0 (0%)	1 (1.4%)	
3-month mRS 0-2	60 (65.2%)	10 (43.5%)	50 (72.5%)	0.02
12-month mRS 0-2	61 (66.3%)	11 (47.8%)	50 (72.5%)	0.04
3-month mortality	4 (4.3%)	3 (13%)	1 (1.4%)	0.047
12-month mortality	9 (9.8%)	5 (21.7%)	4 (5.8%)	0.04
1-year stroke recurrence	7 (8.2%)	4 (19.1%)	3 (4.7%)	0.06
1-year stroke recurrence	15 (9%)	4 (19.1%)	11 (7.5%)	0.10

SUPPLEMENTARY TABLE II: Multivariate analysis for 3 and 12-month functional outcome and 12-month stroke recurrences in the entire and in the matched cohorts. mRS= modified Rankin score; NIHSS= National Institute Health Stroke Scale.

A. Multivariate analysis for 3-month functional independence (mRS 0-2) on the entire cohort

Variable	OR (95%CI)	P-value
Bilateral lesion (vs. unilateral)	0.28 (0.09-0.87)	**0.030**
Age	0.96 (0.93-0.99)	0.010
mRS pre-stroke	0.65 (0.41-1.04)	0.070
Baseline NIHSS	0.79 (0.74-0.86)	**0.000**

B. Multivariate analysis for 3-month functional independence (mRS 0-2) on the matched cohort

Variable	OR (95%CI)	P-value
Bilateral lesion (vs. unilateral)	0.24 (0.06-0.92)	**0.040**
Age	0.96 (0.91-1.01)	0.110
mRS pre-stroke	0.47 (0.25-0.87)	0.020
Baseline NIHSS	0.76 (0.68-0.87)	**0.000**

C. Multivariate analysis for 12-month functional independence (mRS 0-2) on the entire cohort

Variable	OR (95%CI)	P-value
Bilateral lesion (vs. unilateral)	0.45 (0.14-1.50)	**0.190**
Age	0.95 (0.92-0.98)	0.000
Active cancer	0.16 (0.03-0.84)	0.030
mRS pre-stroke	0.44 (0.26-0.74)	**0.000**
Baseline NIHSS	0.79 (0.73-0.86)	0.000

D. Multivariate analysis for 12-month functional independence (mRS 0-2) on the matched cohort

Variable	OR (95%CI)	P-value
Bilateral lesion (vs. unilateral)	0.36 (0.08-1.58)	**0.180**
Age	0.96 (0.91-1.01)	0.130
mRS pre-stroke	0.30 (0.15-0.62)	0.000
Baseline NIHSS	0.74 (0.65-0.85)	**0.000**

E. Multivariate analysis for 12-month stroke recurrence on the entire cohort

Variable	OR (95%CI)	P-value
Bilateral lesion (vs. unilateral)	2.77 (0.77-9.94)	**0.120**
Age	1.01 (0.97-1.04)	**0.760**

F. Multivariate analysis for 12-month stroke recurrence on the matched cohort

Variable	OR (95%CI)	P-value
Bilateral lesion (vs. unilateral)	4.76 (0.97-23.4)	**0.060**
Age	1.00 (0.95-1.06)	**0.900**