

CLINICAL AND POPULATION SCIENCES

Cervical Artery Tortuosity Is Associated With Dissection Occurrence and Late Recurrence: A Nested Case-Control Study

Lukas Mayer-Suess¹, MD, PhD; Michael Knoflach¹, MD; Tamara Peball, MD; Stephanie Mangesius¹, MD, PhD; Ruth Steiger¹, MSc; Sergiy Pereverzyev Jr, MSc, PhD; Hannes Lerchner, BSc; Ludovic Blache, MSc, PhD; Manuel Mayr¹, MD, PhD; Gudrun Ratzinger¹, MD; Stefan Kiechl¹, MD; Elke R. Gizewski¹, MD; Raimund Pechlaner¹, MD, PhD

BACKGROUND: The pathogenesis of spontaneous cervical artery dissection remains unclear, and no established predictors of recurrence exist. Our goal was to investigate the potential association between cervical artery tortuosity, a characteristic of patients with connective tissue disorder, and spontaneous cervical artery dissection.

METHODS: The ReSect study (Risk Factors for Recurrent Cervical Artery Dissection) is an observational study that invited all spontaneous cervical artery dissection patients treated at the Innsbruck University Hospital between 1996 and 2018 for clinical and radiological follow-up. Internal carotid and vertebral artery tortuosity was assessed on magnetic resonance angiography using a validated 3-dimensional algorithm. Differences between patients and healthy controls as well as dependent on recurrence status were assessed by applying χ^2 , Mann-Whitney *U* test, and Kruskal-Wallis test where applicable, and confounders were established by bivariable Pearson correlation. Logistic regression was used to address the impact of tortuosity on dissection occurrence and recurrence as well as its association to extracellular matrix proteome data derived from skin biopsies in a subset of patients.

RESULTS: Magnetic resonance angiography was performed a median of 6.5 years after dissection in the included dissection patients. Patients with dissection ($n=125$) had significantly increased values of internal carotid artery tortuosity compared with healthy controls ($n=24$; odds ratio, 2.65 [95% CI, 1.68–3.86], 1 SD increase; $P<0.01$). This was also true for patients with long-term dissection recurrence ($n=7$) when compared with those with single time-point dissection ($n=118$; odds ratio, 2.00 [95% CI, 1.47–3.99], 1 SD increase; $P<0.01$). In patients with dissection and available extracellular matrix protein data ($n=37$), 6 of 13 (46.2%) proteins previously found linked with dissection recurrence were also associated with increased tortuosity. All 3 proteins associated with both anterior and posterior circulation tortuosity belonged to the desmosome-related cluster.

CONCLUSIONS: Internal carotid artery tortuosity is elevated in spontaneous cervical artery dissection patients compared with healthy controls, and this difference is most pronounced if individuals suffer from long-term dissection recurrence. Additionally, an association between tortuosity, being a readily measurable biomarker in routine magnetic resonance angiography, and proteomic markers of dissection recurrence exists, further enhancing the prospect of underlying subclinical connective tissue disease in dissection patients.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: biopsy ■ cerebrovascular disorders ■ connective tissue ■ magnetic resonance angiography ■ vertebral artery

Correspondence to: Lukas Mayer-Suess, MD, PhD, Department of Neurology, Medical University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria, Email lukas.mayer@i-med.ac.at; or Michael Knoflach, MD, Department of Neurology, Medical University of Innsbruck, Anichstraße 35, A-6020 Innsbruck, Austria, Email michael.knoflach@i-med.ac.at

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.124.049046>.

For Sources of Funding and Disclosures, see page 418.

© 2024 American Heart Association, Inc.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

BMI	body mass index
MRI	magnetic resonance imaging
OR	odds ratio
sCeAD	spontaneous cervical artery dissection

Although spontaneous cervical artery dissection (sCeAD) is among the most common causes of stroke in young patients, its pathogenesis remains unclear, and no established predictors of recurrence exist.^{1,2} It is well known that monogenetic connective tissue disorders, such as Marfan syndrome or Ehlers-Danlos syndrome type IV, are associated with an increased risk of sCeAD.²⁻⁴ The majority of dissection patients, however, do not suffer from monogenetic connective tissue disorders.³ Still, dermal ultrastructural connective tissue alterations visible on electron microscopy and alterations in extracellular matrix proteome composition, especially of individuals with recurrent dissection, suggest a to-date unknown subclinical connective tissue disorder.^{5,6} As a clinical surrogate, increased arterial tortuosity, being the twisting, turning, and meandering of arteries, has been reported in patients with monogenetic connective tissue disorders, which also seems to be higher in patients with recent sCeAD compared with other stroke patients.⁷⁻¹⁴ Whether the increase in cervical artery tortuosity remains stable in the long run and, therefore, may characterize a phenotype of patients prone to dissection remains hitherto unknown. In the present analysis, we compare 3-dimensional cervical artery tortuosity in a large cohort of sCeAD patients with and without dissection recurrence as well as in healthy controls. Furthermore, we explore the degree of association of cervical artery tortuosity with candidate extracellular matrix proteins that have been previously linked to sCeAD recurrence.⁶

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient Cohort

A detailed description of the ReSect study (Risk Factors for Recurrent Cervical Artery Dissection) has been published previously.^{6,15-17} In short, the ReSect study is a single-center cohort study investigating risk markers for sCeAD recurrence. All patients treated at the Medical University of Innsbruck for sCeAD between 1996 and 2018 were invited to a standardized follow-up examination no earlier than 1 year after sCeAD. Dissection diagnosis had to be secured through visualization of vessel wall hematoma in T1 fat-saturated magnetic resonance imaging (MRI) in the acute phase. The follow-up examination

consisted of a detailed patient history, clinical examination, skin punch biopsy, and 3 Tesla MRI with contrast-enhanced angiography of the extra- and intracranial vessels, which adhered to a predefined protocol.¹⁸ A control group of healthy volunteers, free of neurological or vascular disease, was recruited through a study-specific public outreach program using flyers and social media callouts. Each healthy participant underwent the same study protocol as patients with sCeAD to ensure comparability. Extracellular matrix proteome analysis based on skin punch biopsies was performed in a subset of patients and controls. This previous analysis yielded 13 extracellular matrix proteins, consisting of a desmosome-related (Catenin delta-1, Junction plakoglobin, Envoplakin, and Desmoplakin) and collagen-related (Collagen alpha-1 XXII chain, Collagen alpha-1 XII chain, Collagen alpha-2 IV chain, Collagen alpha-2 I chain, Basement membrane-specific heparin sulfate proteoglycan core protein, Elastin, Laminin subunit beta-2, and Microfibrillar-associated protein 5) cluster that were linked to sCeAD recurrence.⁶ The association of these proteins with cervical artery tortuosity is tested within the context of this study.

Variable Definitions

Date of hospital admission due to sCeAD was defined as baseline, while date of study-specific MRI used for tortuosity analysis was considered follow-up. Cerebral ischemia was defined as patients that suffered ischemic stroke or transient ischemic attack due to dissection at baseline. Transient ischemic attack was defined according to a duration of neurological symptoms <24 hours (time-based definition) and was diagnosed by the treating stroke physician. Clinical and functional status of patients were evaluated using the National Institutes of Health Stroke Scale and the modified Rankin Scale. The dissection cohort was grouped into either (1) single time-point sCeAD, being those with a single or multiple vessel dissection diagnosed at the initial baseline MRI, or (2) sCeAD recurrence, being those with another sCeAD event ≥ 6 months after the initial dissection (no study participant had > 2 dissection events). We choose this cutoff to exclude multiple vessel dissections in close temporal proximity that are sometimes overlooked in the acute phase MRI as the mural hematoma has not sufficiently developed and is visible in a follow-up MRI in the postacute phase. Anterior circulation combines both internal carotid arteries, while posterior circulation involves both vertebral arteries.

Vessel Segmentation and Distance Metric Variable Acquisition

Tortuosity was measured using the distance metric, which is defined as the ratio of the vessel centerline length to the straight-line distance between the vessel origin and end point.¹⁹ The method of assessment was standardized and adhered to a previously established and validated method utilizing 3-dimensional magnetic resonance angiography data showing low inter-user variability (<1%).¹⁸

Statistical Analysis

Variables were summarized as count (percentage) or median (first quartile, third quartile). χ^2 , Mann-Whitney *U* test, and Kruskal-Wallis test were used in group comparisons, where applicable.

A principal component analysis applying tortuosity values of all 4 cervical arteries was done to test whether a correlation of tortuosity existed between the assessed vessels (ie, left or right carotid or vertebral artery). In this analysis, we report Kaiser-Meyer-Olkin test of sampling adequacy and Bertlett test of sphericity. Kaiser rule was applied to address components of interest (ie, eigenvalue <1 results in discarding of component), and measures within components with values >0.4 were considered to be correlated. To establish potential confounders, correlation of patient characteristics to individual vessel tortuosity was tested through bivariable Pearson correlation analysis. The impact of tortuosity on dissection occurrence (ie, healthy versus dissection) and dissection recurrence (ie, single time-point versus recurrent dissection) as well as the association between extracellular matrix proteins of interest and measures of tortuosity were analyzed through logistic regression, applying adjustment for confounders established through Pearson correlation. Odds ratios (ORs) represent a magnitude of change per 1 SD. Based on the results of our principal component analysis as well as due to our sample size, within-subject averaging of the vertebral artery (ie, posterior circulation) and internal carotid artery (ie, anterior circulation) was done before regression analysis. *P* values were 2-sided, and an alpha level of 0.05 is used. Analysis was conducted using IBM SPSS Statistics (IBM Corp, Released 2023, IBM SPSS Statistics for Windows, version 29.0.2.0, Armonk, NY).

Standard Protocol Approvals, Registration, and Patient Consents

This analysis was approved by the local ethics committee, and appropriate informed consent of patients and healthy controls who took part in the ReSect study was obtained according to the Declaration of Helsinki. This observational study adheres to Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

RESULTS

A total of 148 patients with sCeAD as well as 26 healthy adults (ie, controls) were recruited to the ReSect study. Eight patients had sCeAD recurrence, which entails an annual recurrence risk of 0.9%. Characteristics of the entire cohort as well as subgroups and controls are shown in Tables 1 and 2.

Healthy controls differed significantly in dissection, while single time-point dissection patients only differed in length of follow-up to those with recurrence.

Tortuosity at our study-specific assessment was available in 125 of 148 (84.5%), 22 of the unavailable individuals had single time point and 1 had recurrent sCeAD) patients with sCeAD and 24 of 26 (92.3%) of healthy controls. The reason for missing data in patients with sCeAD was high-grade stenosis or occlusion masking the magnetic resonance angiography contrast agent, while timing issues of contrast agent application led to low imaging quality in 2 controls. We refrained from multiple imputation procedures and excluded these cases from our analysis. All other values of interest were in ReSect study participants. Table S1 presents descriptive cervical artery

Table 1. Characteristics of Dissection Patients and Healthy Controls

	Dissection	Healthy controls	<i>P</i> value
N	148	26	NA
Tortuosity available*	125 (84.5)	24 (92.3)	0.210
Female*	66 (44.6)	16 (61.5)	0.083
Baseline			
Age, y†	44.3 (36.2–50.3)	NA	NA
Cerebral ischemia*	103 (69.6)	NA	NA
NIHSS admission†	1 (0.0–3.0)	0 (0.0–0.0)	<0.001
Hypertension*	32 (21.6)	0 (0.0)	0.003
Follow-up			
Age†	51.8 (45.3–59.5)	49.3 (38.3–52.6)	0.012
Hypertension*	51 (34.5)	0 (0.0)	<0.001
BMI†	25.6 (22.9–27.7)	24.3 (21.4–27.1)	0.386
Length of follow-up, y†	6.5 (3.7–10.7)	NA	NA
mRS at follow-up†	0 (0–1)	0 (0–0)	<0.001

BMI indicates body mass index; mRS, modified Rankin Scale; NA, not applicable; and NIHSS, National Institutes of Health Stroke Scale.

*Count (proportion).

†Median (first quartile–third quartile).

tortuosity of all subgroups of interest, while Figure 1 illustrates these results on an individual vessel basis.

Internal carotid artery tortuosity was higher in patients with sCeAD compared with healthy adults, while vertebral artery tortuosity was not (Figure 1A). Furthermore, the difference was more pronounced in individuals with long-term dissection recurrence compared with healthy

Table 2. Characteristics of Single Time Point Dissection and Recurrent Dissection Patients

	Single time point	Recurrent	<i>P</i> value
N	140	8	
Tortuosity available*	118 (84.3)	7 (87.5)	0.891
Female*	63 (45.0)	3 (37.5)	0.485
Baseline			
Age, y†	44.7 (36.3–50.7)	43.3 (32.2–45.3)	0.264
Cerebral ischemia*	98 (70.0)	5 (62.5)	0.673
NIHSS admission†	4 (0.5–2.8)	1 (0.0–8.0)	0.599
Hypertension*	31 (22.1)	1 (12.5)	0.604
Follow-up			
Age, y†	51.8 (44.9–59.7)	51.3 (50.1–54.1)	0.869
Hypertension*	50 (35.7)	1 (12.5)	0.311
BMI†	25.6 (22.9–27.7)	25.0 (21.6–28.7)	0.900
Length of follow-up, y†	6.4 (3.7–10.1)	9.6 (7.0–16.3)	0.038
mRS at follow-up†	0 (0–1)	0 (0–1)	0.899

BMI indicates body mass index; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Count (proportion).

†Median (first quartile–third quartile).

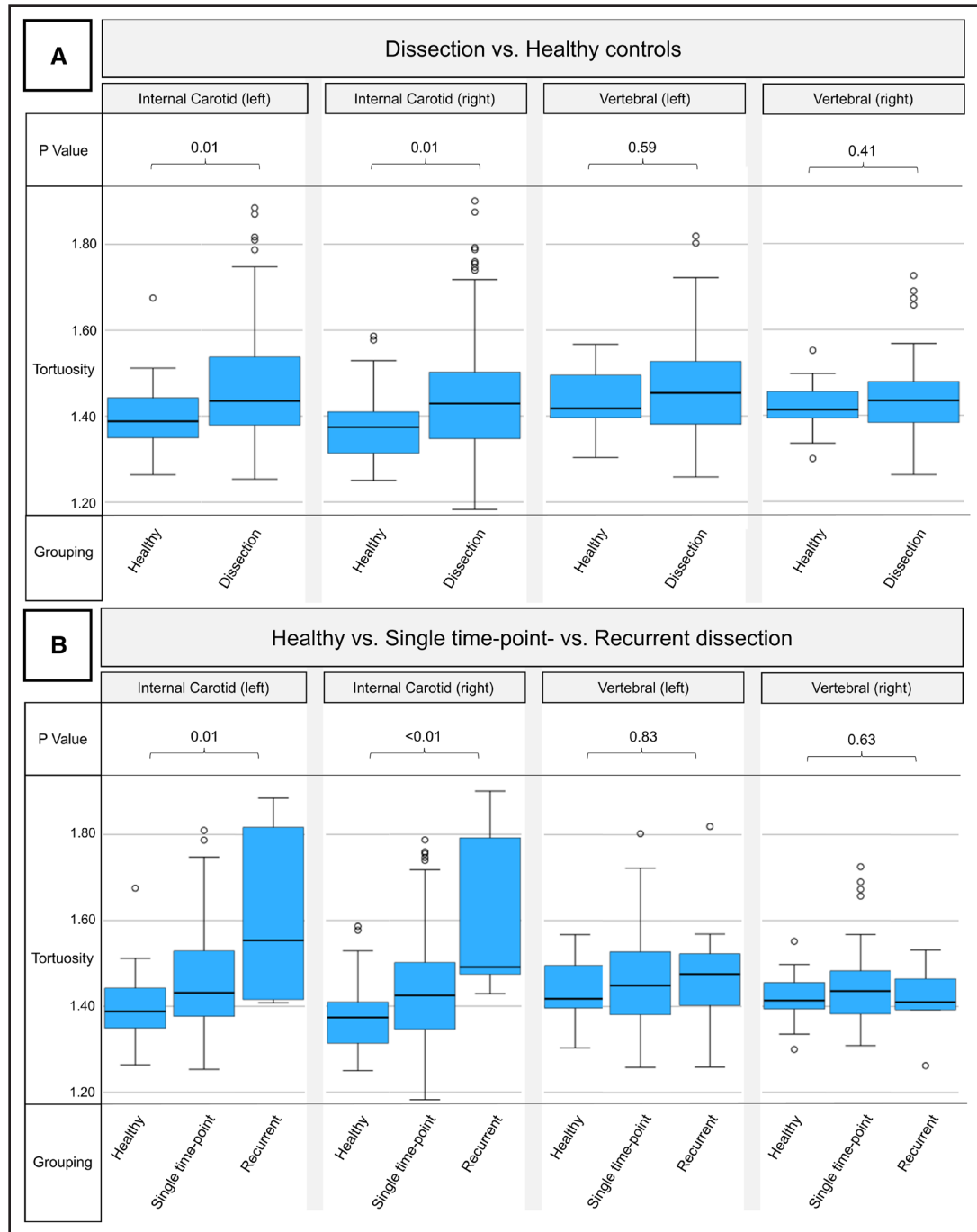


Figure 1. Differences in individual vessel tortuosity.

Comparison of healthy controls vs dissection patients (A) as well as healthy controls vs single time point vs recurrent dissection (B).

controls and single time-point dissection (Figure 1B), which was independent of length of follow-up (data not shown). Pearson correlation revealed that age at follow-up (ie, age at imaging date used for tortuosity measurement) was the only characteristic consistently correlated with cervical artery tortuosity (Table S2) in patients with sCeAD. Logistic regression emphasized that, after adjusting for age, dissection patients were significantly more likely to have higher anterior circulation tortuosity than healthy controls (OR, 2.65 [95% CI, 1.68–3.86], 1

SD increase; $P < 0.01$), but not higher posterior circulation tortuosity (OR, 0.73 [95% CI, 0.16–2.22], 1 SD increase; $P = 0.60$). The same was true when comparing patients with dissection recurrence to those with single time-point dissection (anterior circulation OR, 2.00 [95% CI, 1.47–3.99], 1 SD increase; $P < 0.01$; posterior circulation OR, 0.44 [95% CI, 0.11–2.36], 1 SD increase; $P = 0.44$).

Despite these differences in findings about anterior and posterior circulation tortuosity measurements within our analyses, a principal component analysis revealed

that tortuosity values of all 4 arteries were correlated to each other in a positive manner, meaning that increased tortuosity values of internal carotid arteries correlated to higher tortuosity measures in vertebral arteries and vice versa (Tables S3 and S4).

Adding available extracellular matrix proteome data ($n=37$), 6 of 13 (46.2%) proteins previously found linked with dissection recurrence were associated with either anterior- and posterior-circulation tortuosity in all dissection patients (ie, independent of dissection recurrence; Figure 2). Of interest, all 3 proteins associated with both anterior and posterior circulation tortuosity belonged to the desmosome-related cluster.

Finally, Figure S1 emphasizes that tortuosity values do not show relevant change when excluding the initially dissected vessel at baseline.

DISCUSSION

Key findings of this study are that (1) internal carotid artery tortuosity is elevated in patients with sCeAD years after dissection compared with healthy controls and that (2) this difference is most pronounced if individuals suffer from long-term dissection recurrence (Figure 1). Furthermore, (3) specific extracellular matrix proteins linked to sCeAD recurrence are directly associated with internal carotid as well as vertebral artery tortuosity (Figure 2).

As previous studies to date had only investigated cervical artery tortuosity in patients with recent sCeAD, it was hitherto unknown whether the reportedly elevated value of tortuosity relies on transient changes in vessel architecture caused by sCeAD-related vessel pathologies (ie, stenosis, occlusion, and aneurysm formation), which are

known to potentially recede within months.^{20–23} Our study suggests persistent structural alterations of both internal carotid arteries after sCeAD as indicated by elevated tortuosity at a median of 6.5 years after dissection (Figure 1). When excluding the vessels affected by the index dissection from our analysis, our results remain unaltered (Figure S1), indicating that this increase reflects a general vessel characteristic rather than an effect solely attributable to the vessel dissected at baseline.

Concerning vertebral arteries, tortuosity of these vessels did not relevantly differ between dissection patients (all, single time-point dissections, or individuals with long-term recurrence) and healthy controls (Figure 1). However, our principal component analysis revealed a positive correlation between all 4 investigated arteries in patients with sCeAD, which means that increased tortuosity values in internal carotid arteries correlated to higher tortuosity in vertebral arteries and vice versa, indicating that post-sCeAD tortuosity reflects a general phenomenon involving all cervical arteries. The lack of inter-group differences in tortuosity values of vertebral arteries may stem from the considerably lower variance of tortuosity in the posterior circulation, which is likely a consequence of the anatomic partial entrapment of the vertebral arteries within the foraminal segment leading to a reduced degree of freedom. Larger cohorts might be needed to establish differences in absolute values of tortuosity in the posterior circulation.

In a subgroup of our patient cohort, an association of extracellular matrix proteins, previously linked with sCeAD recurrence, to cervical artery tortuosity was found. Overall, 6 of 13 (46.2%) of these proteins were significantly associated with cervical artery tortuosity, while 3 of

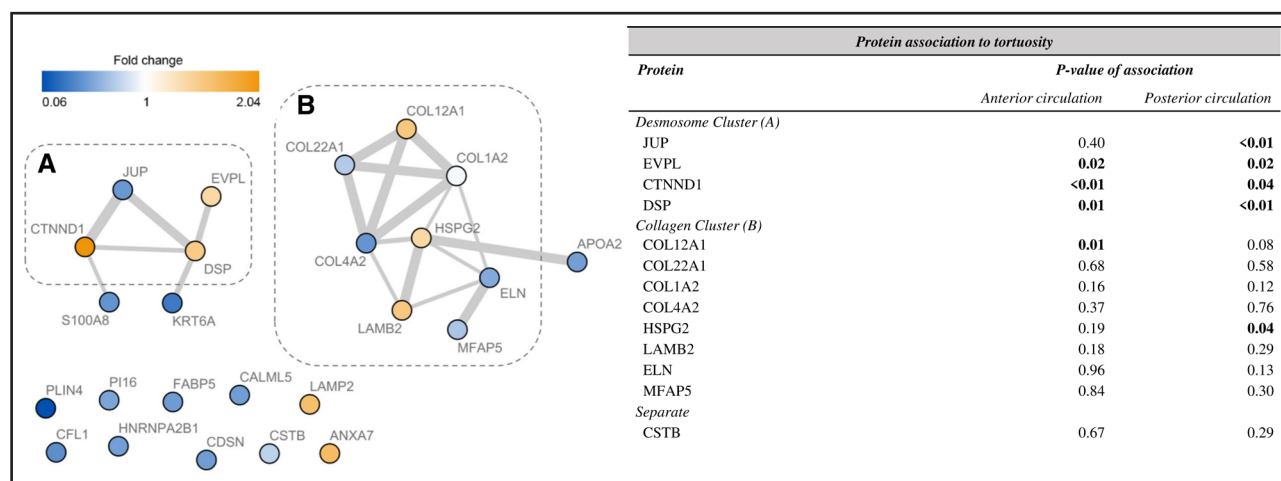


Figure 2. Link between previously established protein markers of dissection recurrence and anterior- as well as posterior-circulation tortuosity.

After the 13 proteins of interest were highlighted in the preconstructed cytoscape network, 2 main clusters were identified: (A) desmosome-associated protein and (B) collagen and elastin cluster (Mayer-Suess et al, Neurology, 2020). COL12A1 indicates collagen alpha-1(XII) chain; COL1A2, collagen alpha-2(I) chain; COL22A1, collagen alpha-1(XXII) chain; COL4A2, collagen alpha-2(IV) chain; CSTB, cystatin-B; CTNND1, catenin delta-1; DSP, desmoplakin; ELN, elastin; EVPL, envloplakin; HSPG2, basement membrane-specific heparan sulfate proteoglycan core protein; JUP, junction plakoglobin; LAMB2, laminin subunit beta-2; and MFAP5, microfibrillar-associated protein 5.

these proteins were associated with both the tortuosity of the anterior circulation (ie, internal carotid artery) and posterior circulation (ie, vertebral artery; Figure 2). All 3 of these proteins associated with both circulations were desmosome-related and embedded in a protein cluster functionally relevant to tissue stability and cell-cell adhesion.⁶ This finding is of special interest, because known hereditary connective tissue disorders (such as Marfan, Ehlers-Danlos, and Louis-Dietz syndromes) are associated with increased cervical artery tortuosity as well as with an increased risk of sCeAD. These rare monogenetic disorders are present in only $\approx 1\%$ of patients with sCeAD in general (none in our cohort).⁶ Yet, an underlying subclinical connective tissue disorder in sCeAD has been suspected for years. For instance, previous studies reported that 55% of patients with sCeAD have structural aberrations in electron microscopy analysis of skin punch biopsies.^{2,24} Our results are in line with the concept of an underlying connective tissue aberration in patients with sCeAD, and with vessel tortuosity offering a readily measurable surrogate for such an aberration.

Strengths of the current study include the use of a validated measure of 3-dimensional cervical artery tortuosity measured in a long-term follow-up of patients with sCeAD and comparison to healthy controls. This is novel as prior studies were limited by either (1) application of 2-dimensional tortuosity measures or visual grading, (2) assessment of tortuosity in the acute phase only, (3) missing information on reliability and reproducibility of the tortuosity measurement, or (4) lack of comparison to healthy controls.^{11–14,25,26} One further novelty lies in relating tortuosity to extracellular matrix protein markers of recurrent dissection. Additionally, the current study is among the largest single-center studies of sCeAD. We acknowledge that our study has limitations concerning (1) sample size, especially of patients with sCeAD recurrence, due to the overall number of patients in the ReSect cohort and loss to follow-up, (2) the lack of standardized longitudinal measurements of tortuosity, (3) information on tortuosity before dissection, and (4) the potential of patients within the single time point dissection subgroup suffering late recurrence. However, late recurrences are seldom, and the annual risk of recurrence is low; the number of misclassified cases probably is insignificant. Furthermore, (5) proteomics data were only available in a subset of patients. As the collection of biosamples (ie, skin) as well as the subsequent proteomic analysis of these samples is difficult and expensive, there is a clear need for large cooperative multicenter efforts to validate and expand on our findings in the future. Finally, (6) controls were not matched to cases; however, the differences were accounted for in adjusting for confounders.

Taken together, we provide evidence that a long-term stable measure of cervical artery tortuosity relates to sCeAD, and we establish an association between tortuosity and proteomic markers of sCeAD recurrence.

Three-dimensional distance metric tortuosity measurement might represent a feasible avenue for stratification of high-risk cohorts, therefore assisting in the design of prospective studies investigating dissection recurrence.

ARTICLE INFORMATION

Received August 21, 2024; final revision received November 5, 2024; accepted November 19, 2024.

Presented in part at the World Stroke Congress, Abu Dhabi, United Arab Emirates, October 23–26, 2024.

Affiliations

Department of Neurology (L.M.-S., M.K., T.P., S.K., R.P.), Department of Radiology (S.M., R.S., S.P., H.L., L.B., E.R.G.), Neuroimaging Research Core Facility (S.M., R.S., S.P., H.L., L.B., E.R.G.), and Department of Dermatology, Venereology and Allergology (G.R.), Medical University of Innsbruck, Austria. VASCage, Research Centre on Clinical Stroke Research, Innsbruck, Austria (M.K., S.K.). National Heart and Lung Institute, Imperial College London, United Kingdom (M.M.).

Sources of Funding

Drs Mayer-Suess and Knoflach's research was funded by the Österreichische Nationalbank Anniversary fund (No. 15644). This study is supported by VASCage, Research Centre on Clinical Stroke Research. VASCage is a COMET Centre within the Competence Centers for Excellent Technologies (COMET) program and funded by the Federal Ministry for Climate Action, Environment, Energy, Mobility, Innovation and Technology, the Federal Ministry of Labour and Economy, and the federal states of Tyrol, Salzburg and Vienna. COMET is managed by the Austrian Research Promotion Agency (Österreichische Forschungsförderungsgesellschaft). FFG Project number: 898252. Dr Pereverzyev, Jr, H. Lercher, and Dr Blache gratefully acknowledge the support of the Austrian Science Fund (FWF): project P 29514-N32.

Disclosures

Dr Mayr reports grants from Foundation Leducq; employment by Medizinische Universität Wien, Imperial College London, and Kings College London; grants from Österreichische Forschungsförderungsgesellschaft and British Heart Foundation. Dr Gizewski reports compensation from Medtronic for other services. The other authors report no conflicts.

Supplemental Material

Tables S1–S4
Figure S1
STROBE Checklist

REFERENCES

1. Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. *Lancet Neurol*. 2009;8:668–678. doi: 10.1016/S1474-4422(09)70084-5
2. Gunduz ME, Kadirvel R, Kallmes DF, Pezzini A, Keser Z. Spontaneous cervical artery dissection: is it really a connective tissue disease? A comprehensive review. *Front Neurol*. 2023;14:1241084. doi: 10.3389/fneur.2023.1241084
3. Debette S, Goeggel Simonetti B, Schilling S, Martin JJ, Kloss M, Sarikaya H, Hausser I, Engelter S, Metso TM, Pezzini A, et al; CADISP-Plus Consortium. Familial occurrence and heritable connective tissue disorders in cervical artery dissection. *Neurology*. 2014;83:2023–2031. doi: 10.1212/WNL.0000000000001027
4. Adham S, Billon C, Legrand A, Domigo V, Denarié N, Charpentier E, Jeunemaitre X, Frank M. Spontaneous cervical artery dissection in vascular Ehlers-Danlos syndrome: a cohort study. *Stroke*. 2021;52:1628–1635. doi: 10.1161/STROKEAHA.120.032106
5. Brandt T, Orberk E, Weber R, Werner I, Busse O, Müller BT, Wigger F, Grau A, Grond-Ginsbach C, Hausser I. Pathogenesis of cervical artery dissections: association with connective tissue abnormalities. *Neurology*. 2001;57:24–30. doi: 10.1212/wnl.57.1.24
6. Mayer-Suess L, Pechlaner R, Barallobre-Barreiro J, Boehme C, Toell T, Lynch M, Yin X, Willeit J, Gizewski ER, Perco P, et al. Extracellular matrix protein signature of recurrent spontaneous cervical artery dissection. *Neurology*. 2020;95:e2047–e2055. doi: 10.1212/WNL.00000000000010710

7. Franken R, El Morabit A, de Waard V, Timmermans J, Scholte AJ, van den Berg MP, Marquering H, Planken NRN, Zwiderman AH, Mulder BJM, et al. Increased aortic tortuosity indicates a more severe aortic phenotype in adults with Marfan syndrome. *Int J Cardiol.* 2015;194:7–12. doi: 10.1016/j.ijcard.2015.05.072
8. Loeys BL, Schwarze U, Holm T, Callewaert BL, Thomas GH, Pannu H, De Backer JF, Oswald GL, Symoens S, Manouvrier S, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med.* 2006;355:788–798. doi: 10.1056/NEJMoa055695
9. Rodrigues VJ, Elsayed S, Loeys BL, Dietz HC, Yousem DM. Neuroradiologic manifestations of Loeys-Dietz syndrome type 1. *AJNR Am J Neuroradiol.* 2009;30:1614–1619. doi: 10.3174/ajnr.A1651
10. Van Laer L, Dietz H, Loeys B. Loeys-Dietz syndrome. *Adv Exp Med Biol.* 2014;802:95–105. doi: 10.1007/978-94-007-7893-1_7
11. Giossi A, Mardighian D, Caria F, Poli L, De Giuli V, Costa P, Morotti A, Gamba M, Gilberti N, Ritelli M, et al. Arterial tortuosity in patients with spontaneous cervical artery dissection. *Neuroradiology.* 2017;59:571–575. doi: 10.1007/s00234-017-1836-9
12. Narrett JA, Aldridge CM, Garrett J, Abdalla B, Donahue J, Worrall BB, Southerland AM. Vertebral artery tortuosity and morphometric characteristics of patients with recurrent cervical artery dissection. *J Stroke Cerebrovasc Dis.* 2022;31:106346. doi: 10.1016/j.jstrokecerebrovasdis.2022.106346
13. Kim BJ, Yang E, Kim NY, Kim MJ, Kang DW, Kwon SU, Kim JS. Vascular tortuosity may be associated with cervical artery dissection. *Stroke.* 2016;47:2548–2552. doi: 10.1161/STROKEAHA.116.013736
14. Kim ST, Brinjikji W, Lehman VT, Carr CM, Luetmer PH, Rydberg CH. Association between carotid artery tortuosity and carotid dissection: a case-control study. *J Neurosurg Sci.* 2018;62:413–417. doi: 10.23736/S0390-5616.16.03790-5
15. Mayer L, Boehme C, Toell T, Dejakum B, Willeit J, Schmidauer C, Berek K, Siedentopf C, Gizewski ER, Ratzinger G, et al. Local signs and symptoms in spontaneous cervical artery dissection: A single centre cohort study. *J Stroke.* 2019;21:112–115. doi: 10.5853/jos.2018.03055
16. Mayer-Suess L, Geiger M, Dejakum B, Boehme C, Domig LM, Komarek S, Toell T, Kiechl S, Knoflach M. Sex-differences in psychosocial sequelae after spontaneous cervical artery dissection. *Sci Rep.* 2022;12:611. doi: 10.1038/s41598-021-04686-7
17. Mayer-Suess L, Frank F, Töll T, Boehme C, Gizewski ER, Ratzinger G, Broessner G, Kiechl S, Knoflach M. Head/neck pain characteristics after spontaneous cervical artery dissection in the acute phase and on a long-run. *Cephalalgia.* 2022;42:872–878. doi: 10.1177/03331024221079298
18. Mayer-Suess L, Peball T, Pereverzyev S Jr, Steiger R, Galijasevic M, Kiechl S, Knoflach M, Gizewski ER, Mangesius S. Cervical artery tortuosity—a reliable semi-automated magnetic resonance-based method. *Quant Imaging Med Surg.* 2024;14:1383–1391. doi: 10.21037/qims-23-1057
19. Ciurică S, Lopez-Sublet M, Loeys BL, Radhouani I, Natarajan N, Vikkula M, Maas AHM, Adlam D, Persu A. Arterial tortuosity. *Hypertension.* 2019;73:951–960. doi: 10.1161/HYPERTENSIONAHA.118.11647
20. Heldner MR, Nedelcheva M, Yan X, Slotboom J, Mathier E, Hulliger J, Verma RK, Sturzenegger M, Jung S, Bernasconi C, et al. Dynamic changes of intramural hematoma in patients with acute spontaneous internal carotid artery dissection. *Int J Stroke.* 2015;10:887–892. doi: 10.1111/ijss.12553
21. Strunk D, Schwindt W, Wiendl H, Dittrich R, Minnerup J. Long-term sonographical follow-up of arterial stenosis due to spontaneous cervical artery dissection. *Front Neurol.* 2021;12:792321. doi: 10.3389/fneur.2021.792321
22. Guillon B, Brunereau L, Biousse V, Djouhri H, Lévy C, Bousser MG. Long-term follow-up of aneurysms developed during extracranial internal carotid artery dissection. *Neurology.* 1999;53:117–122. doi: 10.1212/wnl.53.1.117
23. Pfefferkorn T, Saam T, Rominger A, Habs M, Gerdes LA, Schmidt C, Cyran C, Straube A, Linn J, Nikolaou K, et al. Vessel wall inflammation in spontaneous cervical artery dissection: a prospective, observational positron emission tomography, computed tomography, and magnetic resonance imaging study. *Stroke.* 2011;42:1563–1568. doi: 10.1161/STROKEAHA.110.599548
24. Welby JP, Kim ST, Carr CM, Lehman VT, Rydberg CH, Wald JT, Luetmer PH, Nasr DM, Brinjikji W. Carotid artery tortuosity is associated with connective tissue diseases. *AJNR Am J Neuroradiol.* 2019;40:1738–1743. doi: 10.3174/ajnr.A6218
25. Venturini G, Vuolo L, Pracucci G, Picchioni A, Failli Y, Benvenuti F, Sarti C. Association between carotid artery dissection and vascular tortuosity: a case-control study. *Neuroradiology.* 2022;64:1127–1134. doi: 10.1007/s00234-021-02848-y
26. Saba L, Argiolas GM, Sumer S, Siotto P, Raz E, Sanfilippo R, Montisci R, Piga M, Wintermark M. Association between internal carotid artery dissection and arterial tortuosity. *Neuroradiology.* 2015;57:149–153. doi: 10.1007/s00234-014-1436-x