

Dolichoectasia and Small Vessel Disease in Young Patients With Transient Ischemic Attack and Stroke

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Background and Purpose—We evaluated whether basilar dolichoectasia is associated with markers of cerebral small vessel disease in younger transient ischemic attack and ischemic stroke patients.

Methods—We used data from the SIFAP1 study (Stroke in Young Fabry Patients), a large prospective, hospital-based, screening study for Fabry disease in young (<55 years) transient ischemic attack/stroke patients in whom detailed clinical data and brain MRI were obtained, and stroke subtyping with TOAST classification (Trial of ORG 10172 in Acute Stroke Treatment) was performed.

Results—Dolichoectasia was found in 508 of 3850 (13.2%) of patients. Dolichoectasia was associated with older age (odds ratio per decade, 1.26; 95% confidence interval, 1.09–1.44), male sex (odds ratio, 1.96; 95% confidence interval, 1.59–2.42), and hypertension (odds ratio, 1.39; 95% confidence interval, 1.13–1.70). Dolichoectasia was more common in patients with small infarctions (33.9% versus 29.8% for acute lesions, $P=0.065$; 29.1% versus 16.5% for old lesions, $P<0.001$), infarct location in the brain stem (12.4% versus 6.9%, $P<0.001$), and in white matter (27.8% versus 21.1%, $P=0.001$). Microbleeds (16.3% versus 4.7%, $P=0.001$), higher grades of white matter hyperintensities ($P<0.001$), and small vessel disease subtype (18.1% versus 12.4%, overall P for differences in TOAST ($P=0.018$) were more often present in patients with dolichoectasia.

Conclusions—Dolichoectasia is associated with imaging markers of small vessel disease and brain stem localization of acute and old infarcts in younger patients with transient ischemic attack and ischemic stroke.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00414583.

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Key Words: Fabry disease ■ hypertension ■ infarction ■ stroke ■ white matter

Elongated and dilated intracranial arteries are found in $\leq 12\%$ of stroke patients.^{1,2} This dilatative arteriopathy, termed intracranial arterial dolichoectasia (IADE), most commonly affects the basilar artery (BA).³ The cause of IADE is unknown. Pathologically, disruption of the internal elastic

lamina and rarefaction of the tunica media of large arteries is observed. Previous studies have reported associations between IADE with older age and the presence of vascular risk factors, especially hypertension, smoking, or a history of stroke or myocardial infarction.

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*A list of all SIFAP1 Investigators is given in the [online-only Data Supplement](#).

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IADE is more common in patients with lacunar stroke and white matter disease.^{2,4,5} However, in 20%, no atherosclerotic risk factors are found. In a minority of patients, IADE is seen in conjunction with metabolic and connective tissue disorders.

IADE may cause brain infarction by embolization, in situ thrombosis, or disruption of perforating arteries.

Data on the relationship between dolichoectasia of the BA and small vessel disease (SVD) in younger stroke patients are limited.

We set out to study IADE in a large cohort of young transient ischemic attack (TIA) and ischemic stroke patients enrolled in a screening program for Fabry disease.⁶ In this cohort, we tested whether dolichoectasia was related to vascular risk factors, SVD, microbleeds, and white matter hyperintensities (WMHs) in younger stroke patients. We also studied infarct location in patients with IADE, hypothesizing that posterior circulation infarcts would be more common.

Methods

Study Population

The SIFAP1 study (Stroke in Young Fabry Patients; NCT004414583) enrolled 5023 young (18–55 years) patients with an acute cerebrovascular event in 15 European countries and 47 study centers experienced in stroke care and the main result on the prevalence of Fabry disease and the study's inclusion and exclusion criteria have already been reported.^{6,7}

Stroke Subtyping and MRI Analysis

SIFAP1 included patients with TIA, ischemic stroke, and intracerebral hemorrhage. Intracerebral hemorrhage patients were excluded from the present analyses. Demographic information (age and sex) and vascular risk factors were taken from the mandatory core data set collected by all centers. Investigators at each site classified the cause of stroke according to the TOAST criteria (Trial of ORG 10172 in Acute Stroke Treatment).

MRI of the brain was obtained where possible with the center-specific set of sequences and the study protocol recommended that T2/PD-weighted and FLAIR images and a diffusion-weighted imaging sequence be performed as a minimum. Investigators were also asked to obtain T1 and T2*-weighted sequences, if possible. These data were collected and interpreted centrally in a predefined and standardized manner.

MRI analysis was performed by 3 experienced readers (C.E., F.F., and R.S.) blinded to clinical and demographic data.⁸ The tortuosity of the BA was rated as none, mild (some tortuosity of BA with a deviation from the midline of >5 mm to ≤10 mm), moderate (deviation of BA from midline by >10 mm and diameter >5 mm), or severe (tortuosity with impression of brain stem and diameter >10 mm). The maximum BA artery diameter was also directly measured at its maximum on axial MRI scans.⁹ We did not separate compression of the brain stem because of vertebral artery tortuosity from compression because of BA tortuosity. Compression because of BA tortuosity had to be present. IADE was defined in this study as a moderate-to-severe tortuosity of the BA. The intraclass correlation coefficient for determining tortuosity was 0.621.

The 3 experienced readers also recorded the presence of acute and old ischemic infarcts, the infarct type (lacunar, borderzone, or territorial), infarct size (≤1 cm, ≤half-lobe/structure, >half-lobe/structure), anatomic infarct location, and vascular territories involved. Diffusion-weighted imaging sequences served to identify areas of acute ischemia. Old infarcts were defined as areas of T2 hyperintensity with associated focal atrophy and containing fluid-filled spaces.

WMHs were defined as lesions with high signal intensity on T2-weighted images in the absence of evidence of complete tissue destruction. WMHs were graded according to the Fazekas scale as

deep WMH (0=absent; 1=punctate; 2=early confluent; 3=confluent) and periventricular WMHs (0=absent; 1=pencil-thin lining; 2=halo of ≥5 mm thickness; 3=irregular WMH extending into deep white matter).

The presence and the location of old microbleeds were identified on gradient-echo T2*-weighted images as previously reported.¹⁰ The interrater reliability of MRI interpretations was assessed and indicated substantial to excellent agreement.

Statistical Analysis

Bivariate analysis was performed to compare risk factors and patient characteristics in patients with and without dolichoectasia using random effects logistic regression models to account for center heterogeneity. Age, sex, and center adjustment were additionally performed if characteristics were significantly associated with IADE (Table 1). Multiple random effects logistic regression analysis was performed with the factors that had an associated *P* value <0.1 in bivariate analysis as fixed factors with the center as a random effect and adjustment for sex and age. In the final model (model 2), only significant covariates from the first model were included. Frequencies of IADE among stroke subtypes (TOAST) were compared using random effects binary logistic models. To test the association of WMH (grades 0–3) with IADE ordinal regression models with random effects were used, with the grade of WMH as the dependent variable and the presence of IADE as the independent variable. Two-tailed *P* values of <0.05 were considered significant. No adjustment for multiple testing was applied. All statistical tests were performed with IBM SPSS version 22 and STATA/IC 12.1.

Ethics

All patients or their legal representatives provided written informed consent. All local ethical committees approved the study.

Results

Participants

The presence or absence of IADE could be rated in 3850 of the 4478 patients with TIA or ischemic stroke (86%) in SIFAP1.¹¹ The baseline characteristics of the patients in whom IADE could not be rated were similar to those patients included in study with respect to age, sex, hypertension, and TOAST subtyping (data not shown). Dolichoectasia of the BA was reported in 508 of 3850 patients (13.2%). IADE was rated as moderate in 417 and severe in 91 patients. The median BA diameter was 3 mm (interquartile range, 2–4) in patients with no tortuosity, 3 mm (interquartile range, 2–4) with mild tortuosity, 4 mm (interquartile range, 3–5) with moderate tortuosity, and 5 mm (interquartile range, 4–5.25 mm) with severe tortuosity. BA diameters were higher in patients with more severe grades of tortuosity (*P*<0.001).

Risk Factors

Table 1 details the characteristics of patients with IADE. Older age, male sex, hypertension, diabetes mellitus, hyperlipidemia, abdominal girth, regular alcohol use, and higher serum creatinine were more common in patients with IADE. In multiple regression models (Table 2), older age, male sex, and hypertension were independently associated with the finding of dolichoectasia. Higher degrees of IADE were more often present in patients with hypertension compared with patients without hypertension (moderate: deviation >10 mm, or diameter >5 mm, 12.9% versus 9.1%, severe: tortuosity with impression of brain stem and diameter >10 mm, 3.5% versus 1.4%; *P*=0.032 adjusted for age, sex, and center, heterogeneity).

Table 1. Characteristics of TIA/Ischemic Stroke Patients With Dolichoectasia

Characteristic	IADE (n=508)	No IADE (n=3342)	Unadjusted, P Value	Age and Sex-Adjusted P Value
Age, y, Median (IQR)	48 (43–52)	46 (40–51)	<0.001	<0.001
Male sex (%)	374 (73.6%)	1904 (57.0%)	<0.001	<0.001
Hypertension (n=3830)	290 (57.2%)	1483 (44.6%)	<0.001	0.001
Diabetes mellitus (n=3832)	70 (13.9%)	316 (9.5%)	0.003	0.072
Hyperlipidemia (n=3704)	203 (41.7%)	1053 (32.7%)	<0.001	0.038
Atrial fibrillation (n=3816)	13 (2.6%)	72 (2.2%)	0.590	...
Congestive heart failure (n=3815)	7 (1.4%)	29 (0.9%)	0.330	...
Abdominal girth (waist circumference in cm, Mean [SD]; n=3740)	97 (16)	94 (15)	<0.001	0.140
Systolic blood pressure (n=3850) mm Hg, mean (SD)	135 (20)	132 (20)	0.001	0.156
Diastolic blood pressure (n=3850) mm Hg, mean (SD)	81 (13)	79 (12)	0.002	0.164
Current smoking, or quit within last 5 y (n=3811)	295 (58.8%)	1805 (54.5%)	0.065	...
Regular alcohol consumption (≥1/wk) (n=3798)	295 (58.8%)	1678 (50.9%)	0.001	0.136
Previous myocardial infarction(s) (n=3831)	12 (2.4%)	103 (3.1%)	0.386	...
Peripheral arterial occlusive disease (n=3815)	6 (1.2%)	76 (2.3%)	0.121	...
Stroke or TIA history (n=3850)	85 (16.7%)	566 (16.9%)	0.842	...
Migraine (n=3761)	99 (20.2%)	684 (20.9%)	0.662	...
Creatinine in μmol/L, median (IQR; n=3083)	77 (67–90)	75 (65–88)	0.003	0.385

IADE indicates intracranial arterial dolichoectasia; IQR, interquartile range; and TIA, transient ischemic attack.

Etiologic Subtypes

TOAST subtypes were determined in 3748 patients with TIA or ischemic stroke. The cause of the index stroke was large artery disease in 605 (16.1%), cardioembolism in 583 (15.6%), SVD in 492 (13.1%), other determined causes in 623 (16.6%), and undetermined cause in 1445 (38.6%) patients. Figure 1 shows the distribution of TOAST categories according to the presence or absence of IADE. There was a significant difference in the frequency of IADE according to TOAST categories ($P=0.018$) mainly because of a higher prevalence of SVD patients with dolichoectasia (18.1%) compared with 12.4% in those without (Figure 1). This association was not significant after adjustment for age and sex ($P=0.168$).

Infarction Location and Size

Acute Infarctions

Acute infarctions were more commonly located in the vertebrobasilar territory in patients with IADE (21.5% versus 14.7%, $P<0.001$). There was no significant preponderance of acute infarctions in the posterior cerebral artery territory in patients with IADE (11.8% in IADE patients versus 9.5% without IADE, $P=0.106$).

The anatomic location of acute lesions was different in IADE and non-IADE patients (Figure 2A). Acute lesions were more commonly identified in the brain stem (12.4% versus 6.9%, $P<0.001$) and white matter (27.8% versus 21.1%, $P=0.001$) and less often in corticosubcortical regions (31.1% versus 34.3%, $P=0.157$) in patients with IADE than in those without IADE.

Acute lacunar infarctions were more common with IADE (16.3% versus 13.3%, $P=0.052$). Similar associations were found for acute (33.9% versus 29.8%, $P=0.065$) small (≤ 1 cm) lesions.

Old Infarctions

Old infarctions were more commonly located in the vertebrobasilar territory in patients with IADE (13.2% versus 8.2%, $P<0.001$). There was a higher frequency of old infarctions in the posterior cerebral artery territory (5.9% in IADE patients versus 3.9% in non-IADE patients, $P=0.040$).

The anatomic location of old infarctions was different in IADE and non-IADE patients (Figure 2B). Old lesions occurred more commonly in brain stem (7.3% versus 2.7%, $P<0.001$), basal ganglia (19.5% versus 9.5%, $P<0.001$), thalamus (6.3% v. 3.3%, $P=0.001$), and white matter (16.1% versus 9.4%, $P<0.001$) in patients with IADE.

Old lacunar infarctions were more commonly identified with IADE (23.0% versus 12.3%, $P<0.001$). Similar associations were found for old, small (≤ 1 cm) lesions (29.1% versus 16.5%, $P<0.001$). Significant associations between IADE and small old lesions and old lacunar infarcts remained after adjustment for age, sex, and hypertension (both $P<0.001$).

Higher degrees of IADE were more often present in patients with acute or chronic brain stem lesions compared with patients without brain stem lesions (moderate: deviation >10 mm, or diameter >5 mm, 15.8% versus 10.3%, severe: tortuosity with impression of brain stem and diameter >10 mm, 7.0% versus 1.8%; $P<0.001$ adjusted for age, sex, and center heterogeneity).

Table 2. Mixed Logistic Regression for Characteristics Associated With Intracranial Arterial Dolichoectasia

	Model 1 (n=3684 Patients/46 Centers)	Model 2 (n=3830 Patients/46 Centers)
	OR (95% CI)	OR (95% CI)
Fixed effects		
Age (in decades)	1.23 (1.07–1.42)	1.26 (1.09–1.44)
Male sex	1.91 (1.54–2.37)	1.96 (1.59–2.42)
Hypertension	1.36 (1.09–1.68)	1.39 (1.13–1.70)
Hyperlipidemia	1.15 (0.93–1.42)	...
Diabetes mellitus	1.08 (0.81–1.48)	...
Random effects		
	β (SE)	β (SE)
Variance between centers	0.17 (0.09)	0.19 (0.09)

In model 2, only significant fixed effects identified in model 1 were included. CI indicates confidence interval; and OR, odds ratio.

White Matter Hyperintensities

Compared with patients without IADE, those with IADE were more likely to have higher grade 2 or 3 WMHs in the deep white matter (21.3% versus 10.6%, $P<0.001$), periventricular white matter (16.7% versus 6.8%, $P<0.001$), or in the pons (7.2% versus 2.4%, $P<0.001$). These findings remained significant after adjustment for age, sex, and hypertension (all P values <0.001).

Cerebral Microbleeds

There was a strong association between IADE and the presence of microbleeds on T2*-weighted MRI. Of the patients with IADE, 16.3% [33/202] had microbleeds at any location compared with 4.7% [65/1372] of the patients without IADE. This association remained significant after correction for age, sex, and hypertension ($P<0.001$).

Microbleeds were more common in corticosubcortical areas (10.7% versus 2.6%, $P<0.001$), deep regions (6.7% versus 2.3%, $P<0.001$), and in the brain stem (7.7% versus 1.8%, $P<0.001$) in patients with IADE versus those without IADE (Figure 3).

Discussion

In the large, multicentre SIFAP1 study, in which detailed TIA/stroke subtyping and independent central review of all MRI scans was performed, 13% of younger TIA or ischemic stroke patients ≤ 55 years of age were found to have dolichoectasia of the BA. This is very similar to the reported frequency of dolichoectasia of 12% in patients with brain infarcts and of 17% in patients with posterior circulation infarcts in a previous moderately sized series of unselected ischemic stroke patients.² Given the young age, the prevalence of IADE in our cohort was surprisingly high.

Dolichoectasia was associated with the presence of vascular risk factors. Our study confirmed the findings of a smaller case-control study of 63 cases of IADE that showed that increasing age, male sex, and hypertension were independently associated with the presence of IADE.² A history of myocardial infarction was also a risk factor in that previous study, but was not observed in SIFAP1, probably because of the younger age and much lower prevalence of ischemic heart disease in our cohort. Previous studies suggested that smoking and hyperlipidemia are associated with IADE, but we did not confirm these findings in this study.^{12,13} This might be because of different risk factor definitions or different exposures in this much younger population.

In unadjusted analyses, patients with dolichoectasia had a higher frequency of SVD, similar to previous reports.^{4,5,13,14} In previous series, the mean age was between 60 and 78 years, compared with 48 years in our study. The association between

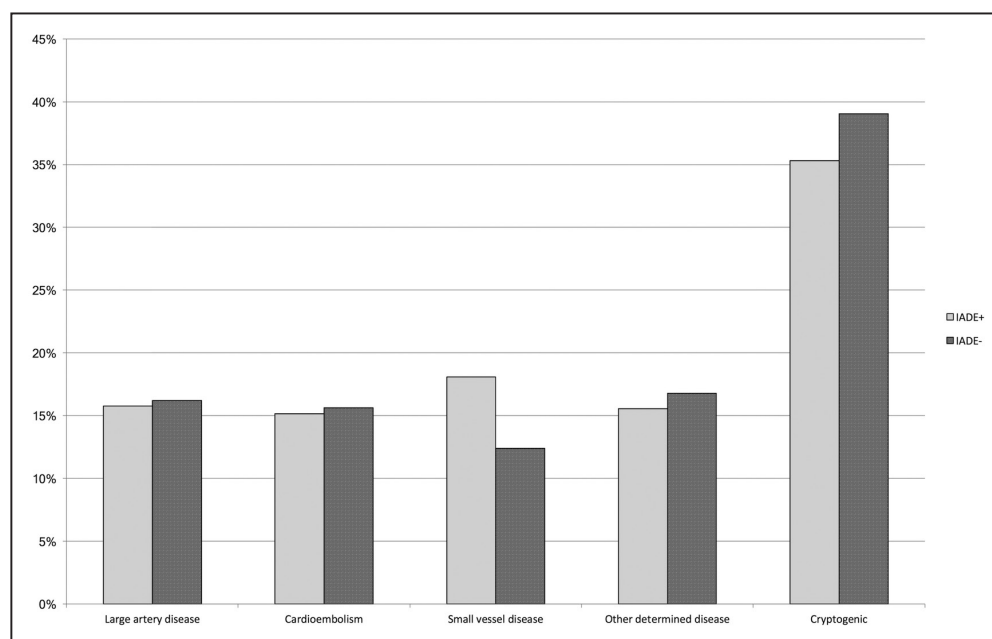


Figure 1. Frequency of TOAST subtypes (Trial of ORG 10172 in Acute Stroke Treatment) in transient ischemic attack and ischemic stroke patients, stratified by the presence of intracranial arterial dolichoectasia (IADE). The overall distribution of TOAST is different with a preponderance of small vessel disease with IADE ($P=0.018$).

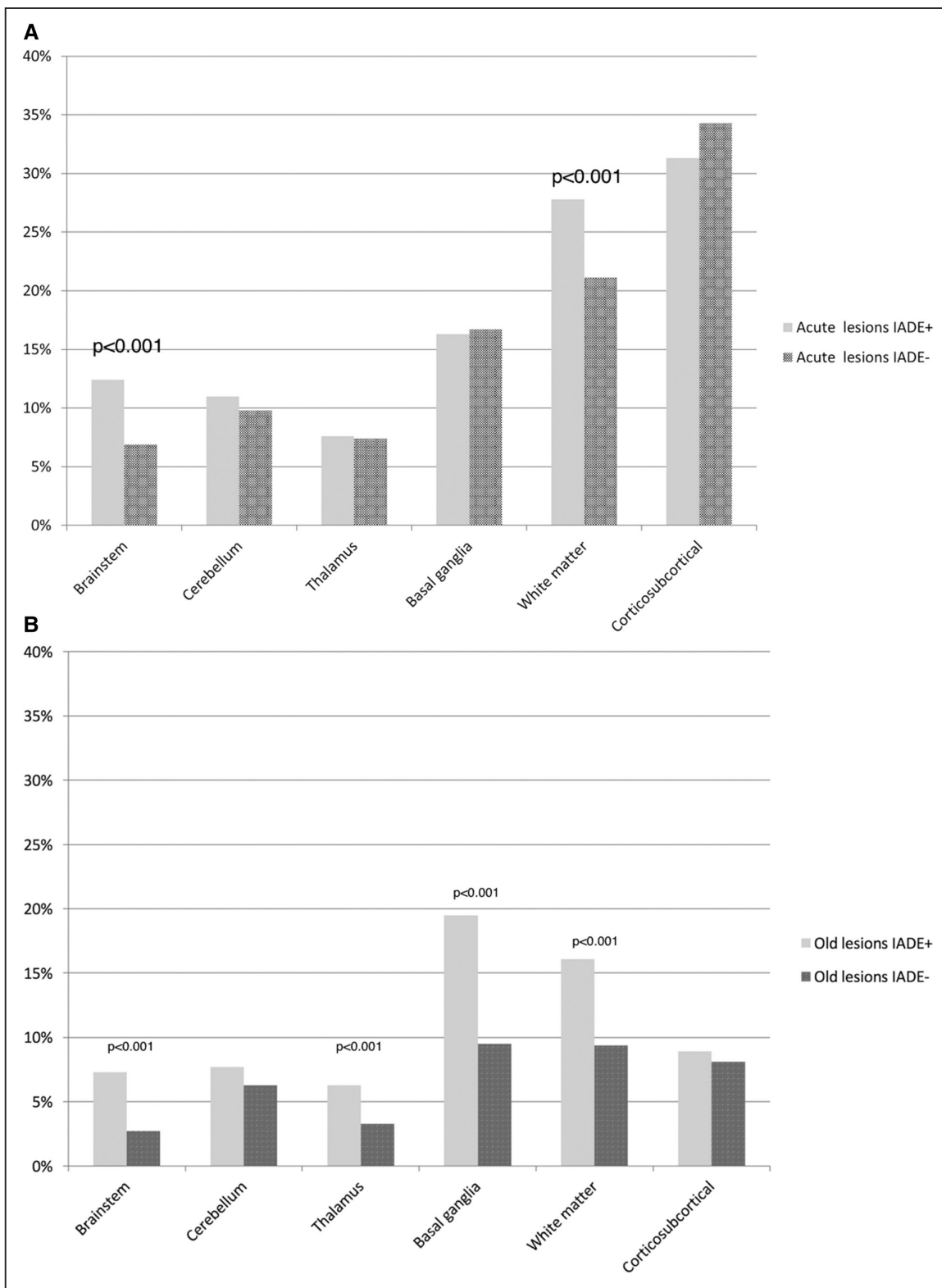


Figure 2. A, Distribution of (sub)acute ischemic lesions according to intracranial arterial dolichoectasia (IADE) status. B, Distribution of old ischemic lesions according to IADE status.

IADE and SVD is further supported by a higher frequency of small infarctions on analyses restricted to MRI data and the higher prevalence of IADE in patients with more severe WMHs. Small infarctions were more commonly located in

the vertebrobasilar territory, but the majority of infarctions in patients with dolichoectasia occurred outside the vertebrobasilar territory and could not be directly attributed to the IADE. The association with imaging markers of SVD

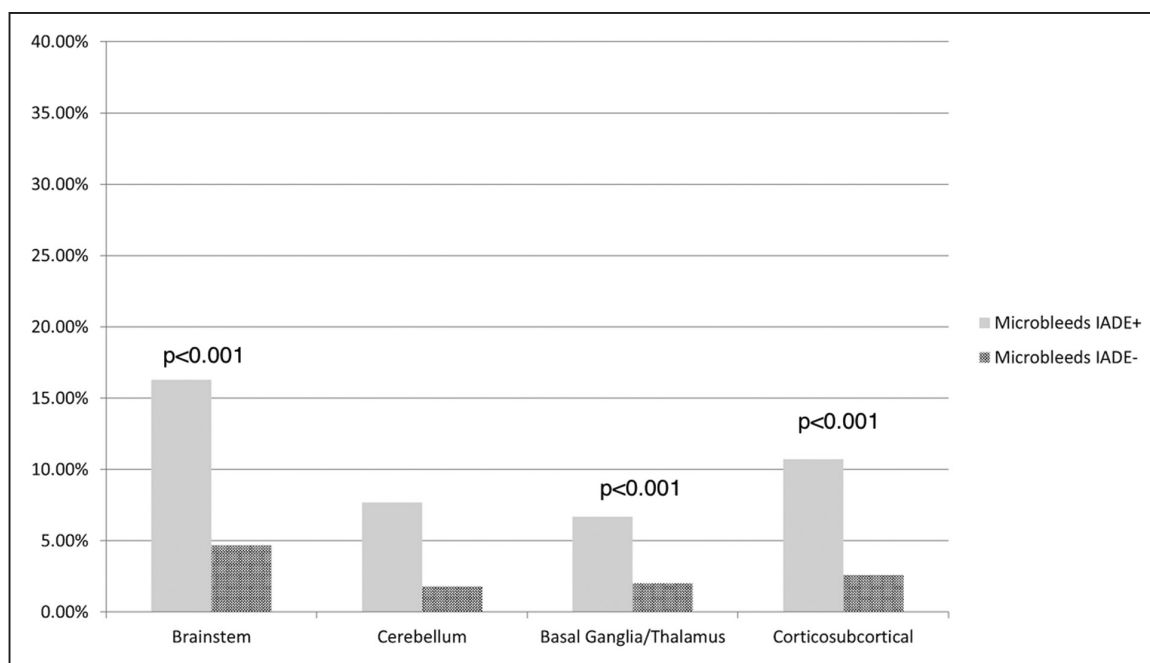


Figure 3. Distribution of cerebral microbleed on GRE according to intracranial arterial dolichoectasia (IADE) status.

suggests a common pathophysiological process affecting the media of the vessels in patients with SVD and IADE. Further studies are needed to confirm previous associations with matrix metalloproteinases and to find other mediators of these arteriopathies.¹⁵

In our study, IADE was associated with cerebral microbleeds (CMBs), another manifestation of SVD.¹⁶ One small series of 28 patients with IADE in an Asian population reported a higher frequency of CMB in IADE patients.¹⁷ In 1 study from Japan, CMBs were associated with increasing BA diameter,¹⁸ and intracranial hemorrhage is a common complication of IADE.¹⁹ Interestingly, in our study, IADE patients also had more lobar microbleeds, which are typically considered to reflect underlying cerebral amyloid angiopathy, but a previous neuropathologic study did not identify cerebral amyloid angiopathy in patients with IADE.¹⁴ Therefore, we have no evidence that cerebral amyloid angiopathy contributes to the development of IADE to date.

On the whole, it seems appropriate to include IADE in the spectrum of conditions associated with markers of SVD, with the proviso that cerebral amyloid angiopathy and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy are not associated with IADE. Dolichoectasia has also been observed in patients with collagen 4 type 1 or 2 gene (COL4A1/2) mutations.²⁰

Our study has several limitations. We did not assess for compressive symptoms, such as cranial nerve palsies or other manifestations of dolichoectasia (eg, hydrocephalus) in our patient population. In our analysis, we focused exclusively on patients with ischemic symptoms. A stronger correlation between IADE and CMB may be present in patients who present with intracerebral or subarachnoid hemorrhage. The identified differences between patients with and without IADE, although statistically significant, were relatively

small. We did not specifically investigate whether nonatherosclerotic diseases, such as connective tissue disorders, were associated with dolichoectasia of the BA. However, we previously reported that in the stroke patients in whom Fabry disease was identified in SIFAP1, IADE was not more frequent than patients without Fabry disease.⁹ SIFAP1 is a hospital-based study that was performed in secondary and tertiary referral academic centers, and this may have led to some selection bias. MRA confirmation of dolichoectasia was not present in all cases. We did not study the abdominal or coronary arteries for the presence of ectasia that may coexist with IADE. We also did not specifically study the subgroup of patients with congenital hypoplastic vertebral arteries on 1 side where BA tortuosity may be severe. Finally, because there is no consensus on the optimal method of identifying and measuring IADE of the vertebrobasilar arteries, one cannot directly compare our findings with those from other studies that used different definitions.²¹ We also were not able to reliably rate dolichoectasia in the anterior circulation.

In conclusion, dolichoectasia of the BA is identified in an important proportion of younger patients with TIA or ischemic stroke in Europe and is more common with increasing age, male sex, and in patients with hypertension. The presence of basilar dolichoectasia seems to increase the likelihood of having vertebrobasilar territory infarction and may well share a common etiopathogenesis with cerebral SVD and CMBs.

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Disclosures

Dr Thijs serves on scientific advisory boards for Bayer, Boehringer Ingelheim, and Pfizer; serves on the editorial boards of *Stroke*, *International Journal of Stroke*, the *European Journal of Stroke*, *European Journal of Emergency Medicine*, and *Acta Neurologica Belgica*; and has received speaker honoraria and support from Bayer, Boehringer Ingelheim, Pfizer, Sygnis, and Daichi Sankyo. Dr Enzinger has received travel grants and speaker honoraria from Biogen-Idec, Teva-Aventis, Merck Serono, Novartis, Bayer-Schering, and Genzyme—a Sanofi company; has served as consultant for Biogen-Idec, Bayer-Schering, Genzyme—a Sanofi company, and Novartis; and has received unrestricted research grants from Teva-Aventis, Biogen-Idec, and Merck Serono. Dr Fazekas serves on scientific advisory boards for Bayer-Schering, Biogen Idec, Genzyme, Merck Serono, Pfizer, Novartis, Perceptive Informatics, and Teva Pharmaceutical Industries Ltd; serves on the editorial boards of *Cerebrovascular Diseases*, *Multiple Sclerosis*, the *Polish Journal of Neurology and Neurosurgery*, *Stroke*, and the *Swiss Archives of Neurology and Psychiatry*; and has received speaker honoraria and support from Biogen Idec, Bayer Schering, Merck Serono, Novartis, Sanofi-Aventis, Shire, and Teva Pharmaceutical Industries Ltd. Drs Tatlisumak and Putaala are supported by a research grant from the Helsinki University Central Hospital Research Fund for research on stroke in the young. Dr Putaala is supported by the The Finnish Medical Foundation. Dr McCabe research programme during this study was funded by the Irish Institute of Clinical Neuroscience-Serono Fellowship programme, Ireland; The Meath Foundation, Ireland; The Vascular Neurology Research Foundation, Ireland; Lundbeck Neurosciences Bursary programme, Ireland; and The Stanley Thomas Johnson Foundation. Dr McCabe research programme was also supported by unrestricted educational grant funding from Bayer Schering, Ireland; Merck Serono, Ireland, Brennan and Company, Ireland; Pfizer, Ireland; Biogen Idec, Ireland; Sanofi-Aventis, Ireland; Elitech, United Kingdom, and was part funded by grant support from the Programme for Research in Third Level Institutions in Ireland (cycle 4), cofunded by the European Regional Development Fund. The other authors report no conflicts.

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Dolichoectasia and Small Vessel Disease in Young Patients With Transient Ischemic Attack and Stroke

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