

Sex differences in the epidemiology of spontaneous and traumatic cervical artery dissections

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ABSTRACT

Background Recent studies show cervical artery dissection (CeAD) is equally common between sexes, and that the incidence of CeAD has risen at a greater rate in females than males. In this population-based study, we identify sex differences in patients diagnosed with spontaneous and traumatic CeAD.

Methods 144 patients with spontaneous or traumatic CeAD were studied for sex differences in medical comorbidities, presenting symptoms and outcomes.

Results Females were more likely to carry a diagnosis of migraine, while males were more likely to have hyperlipidaemia. Females were more likely to present with neck pain, males with stroke. Females were significantly more likely to develop recurrent dissections in the study period.

Conclusions These findings underscore the importance of understanding CeAD through the lens of sex differences and may explain the significant rise in the diagnosis of CeAD in females. These findings support the importance of considering sex-specific risk factors and medical comorbidities with sex predilection in the diagnosis and management of CeAD. Furthermore, it emphasises the importance of female patients understanding risk factors and presenting signs that should prompt evaluation for CeAD.

Recent epidemiology studies have shown that cervical artery dissection (CeAD), previously thought to have male predominance, is equally common across the sexes.¹ Furthermore, over the last several decades, the incidence of CeAD has risen at a greater rate in females than males.² Despite these changes, sex differences in CeAD epidemiology have not been reevaluated. In this population-based study, we sought to identify sex differences in the epidemiology, presentation and natural history of patients diagnosed with spontaneous and traumatic CeAD in Olmsted County, seen at a single centre with a high likelihood of complete case ascertainment, from the years 2002 to 2020.²

Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, 144 patients were included in the study, the findings which are detailed in [table 1](#). Sixty-eight patients were female (47.2%); 76 patients were male (52.8%). There was

no significant difference in age at dissection between females (47.3 years) and males (52.5 years, $p=0.0605$). There was no sex difference in the aetiology or vessel of dissection.

Evaluating medical comorbidities revealed several sex differences. Females were significantly more likely to carry a diagnosis of migraine (55.9% in females vs 15.8% in males, $p<0.001$), while males were significantly more likely to have hyperlipidaemia (43.4% in males vs 26.5% in females, $p=0.034$). There were no differences in other baseline characteristics evaluated.

Individuals were incidentally found to have CeADs without symptoms at equal rates. Females were significantly more likely to present with neck pain (39.7% vs 21.1% in males, $p=0.015$), while presenting symptoms of headache, Horner's syndrome, and pulsatile tinnitus were not different between sexes. While there was no sex predilection for patients presenting with symptoms of stroke lasting less than 24 hours (transient ischemic attack, TIA, symptoms), males were more likely to present with clinical or imaging findings consistent with stroke (57.9% of males compared with 26.5% of females, $p=0.049$), and females were more likely to develop recurrent dissections in the intervening observation period (11.8% vs 1.3%, $p=0.013$). There was no significant sex difference between acute therapy (thrombolysis, $p=0.370$; thrombectomy, $p=0.498$ or hyperacute stenting, $p=0.498$), rates of endovascular intervention ($p=0.463$) or initial antithrombotic choice ($p=0.066$). Regarding long-term therapy, females were more likely to be prescribed aspirin >81 mg/day (22.1% vs 5.3% in males) and males more likely to be prescribed aspirin 81 mg/per day (73.7% vs 50.0%, $p=0.010$). There was no difference in functional outcome at 2 years.

The findings of this study underscore the importance of understanding the natural history of CeAD through the lens of sex differences and may explain the significant rise in the diagnosis of CeAD in female patients over the last several decades.² Previous studies



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Table 1 Sex differences in the epidemiology of spontaneous and traumatic cervical artery dissections, Olmsted County, 2002–2020

	Female (n=68)	Male (n=76)	P
Age at dissection, mean±SEM	47.3±2.0	52.5±1.8	0.0605
Race†			0.701
Asian	3 (4.4)	3 (3.9)	
Black/African American	1 (1.5)	0 (0)	
White	63 (92.6)	69 (90.8)	
Other	1 (1.5)	2 (2.6)	
Unknown/not reported	0 (0)	2 (2.6)	
Ethnicity†			0.371
Hispanic or Latina/o	0 (0)	2 (2.6)	
Not Hispanic or Latina/o	67 (98.5)	71 (93.4)	
Unknown/not reported	1 (1.5)	3 (3.9)	
Aetiology of dissection			0.341
Major trauma	7 (10.3)	14 (18.4)	
Minor trauma	13 (19.1)	11 (14.5)	
Spontaneous	48 (70.6)	51 (67.1)	
Location†			0.081
Common carotid	1 (1.5)	4 (5.3)	
Internal carotid	28 (41.2)	43 (56.6)	
Vertebral	36 (52.9)	28 (36.8)	
Both (carotid and vertebral)	3 (4.4)	1 (1.3)	
Medical comorbidities			
Migraine	38 (55.9)	12 (15.8)	< 0.001**
Hypertension	18 (26.5)	31 (40.8)	0.070
Hyperlipidaemia	18 (26.5)	33 (43.4)	0.034*
Diabetes mellitus†	3 (4.5)	10 (13.2)	0.086
Smoking, current or history	25 (36.8)	33 (43.4)	0.416
Connective tissue disorder or fibromuscular dysplasia†	5 (7.4)	2 (2.6)	0.255
Presenting symptoms and signs			
Asymptomatic	10 (14.7)	13 (17.1)	0.695
Neck pain	27 (39.7)	16 (21.1)	0.015*
Headache	31 (45.6)	37 (48.7)	0.710
Horner's syndrome	11 (16.2)	8 (10.5)	0.317
Transient ischemic attack (TIA)	12 (17.6)	7 (9.2)	0.135
Stroke	18 (26.5)	32 (57.9)	0.049*
Pulsatile tinnitus†	8 (11.8)	3 (3.9)	0.115
Dissection features			
Occlusion	14 (20.6)	22 (28.9)	0.247
Intramural haematoma	20 (29.4)	16 (21.1)	0.247
Dissecting pseudoaneurysm	21 (30.9)	13 (17.1)	0.052
Intraluminal thrombus†	1 (1.5)	5 (6.6)	0.126
Tapering off stenosis	16 (23.9)	26 (34.7)	0.160
Recurrent TIA/stroke†	3 (4.5)	7 (9.5)	0.332
Recurrent dissection†	8 (11.8)	1 (1.3)	0.013*
mRS at 2 years†			0.403

Continued

Table 1 Continued

	Female (n=68)	Male (n=76)	P
0	33 (48.5)	26 (34.2)	
1	22 (32.4)	27 (35.5)	
2	4 (5.9)	9 (11.8)	
3	2 (2.9)	4 (5.3)	
4	6 (8.8)	6 (7.9)	
5	0 (0)	0 (0)	
6	1 (1.5)	4 (5.3)	

Values are represented as n (%) unless otherwise specified. Categorical variables were analysed using χ^2 square or Fisher's exact based on sample size. Continuous variables were analysed using unpaired t-test.

*p<0.05; **p<0.001.

†Fisher's exact testing performed due to sample size.

mRS = modified Rankin Scale for neurologic disability; 0: no symptoms at all, 1: no significant disability despite symptoms; able to carry out all usual duties and activities, 2: slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance, 3: moderate disability; requiring some help, but able to walk without assistance, 4: moderately severe disability; unable to walk and attend to bodily needs without assistance, 5: severe disability; bedridden, incontinent and requiring constant nursing care and attention, 6: dead.

have suggested a younger age of females with CeAD and a male predilection towards traumatic dissection, both of which were not replicated in the current findings.^{1 3 4} It is possible that increased accessibility to vascular imaging over time has led to the diagnosis of dissections that may have been misdiagnosed as migraine or neck pain in the past, knowing that pain is evaluated and treated differently based on sex, and often gender, biases.⁵

Additionally, ischaemic stroke was more common in males. The exact underlying mechanism is not clear, but factors such as a higher burden of vascular risk factors and/or certain dissection features may contribute to a higher risk of ischaemic stroke in males. Although our study failed to show a significant difference in the morphology of dissection potentially due to small sample size, there was a trend towards more pseudoaneurysm formation (outward growth) in females versus stenosis or occlusion (inward growth) in males. This finding is consistent with previous studies showing a higher incidence of aneurysm and pseudoaneurysm in females, and female sex as an independent risk factor for aneurysm growth.⁶⁻⁸ We speculate that dissection morphology contributes to a higher ischaemic event rate in males and more common pain-predominant presentation in females, but further mechanistic studies are needed to validate this hypothesis. While the currently available imaging makes further characterisation of dissection size and morphology challenging, the development of techniques such as high-resolution photon CT angiogram may facilitate these investigations in the future.⁹

It is important for providers to consider sex-specific risk factors, such as pregnancy and oral contraceptive use in the approach to patient who may have CeAD. Pregnancy and the postpartum period have been shown to increase the risk of CeAD more than fivefold,¹⁰ which may be due to hormonally influenced vascular changes, including arterial elasticity and increased wall stiffness¹¹⁻¹³ and

hypertensive disorders of pregnancy,^{14 15} while recent data suggest combined oral contraceptive use may increase risk of CeAD by influencing vascular tone and contributing to arterial stiffness.¹⁶⁻¹⁹ Similarly, medical comorbidities with sex predilection shown to be independent risk factors for spontaneous CeAD, such as fibromuscular dysplasia (higher prevalence in females) and migraine (twofold to threefold more prevalent in females) should be considered.^{10 20-22} Unfortunately, little is understood about outcomes stratified by these risk factors at this time.

Females undergo chiropractic manipulation more than males, which should be considered when facing a female patient with symptoms concerning for CeAD.¹ Understanding sex-specific risk factors highlights the tendency to evaluate individuals with vascular risk factors (ie, hyperlipidaemia, more common in males) for vascular aetiologies of their symptoms and signs, versus deferring further investigation in those with comorbidities either less traditionally associated with stroke or mimickers of its presentation (ie, migraine, more common in females).⁴ Interestingly, a systematic review of risk factors for CeAD showed that traditional vascular risk factors were less likely to be associated with CeAD than non-CeAD ischaemic stroke, while migraine has demonstrated a strong association in both non-CeAD ischaemic stroke and healthy controls.²³ Differences in practice based on sex-based norms may lead to underdiagnosis and, therefore, underrepresentation of females with CeAD. Our findings also highlight the sex-dependent risk of CeAD recurrence in females, which may impact decisions regarding follow-up and prevention strategy.

Although our study has the strength of complete case ascertainment, inclusion of just one centre and county in the USA with notably high rates of non-Hispanic whites is a limitation for generalisability to more diverse populations.² The small sample size is another limitation, which did not allow for a thorough investigation of underlying

mechanisms of sex differences and antithrombotic treatment decisions, which should be the focus of future investigation.

As important as it is for clinicians to understand the role of sex in the presentation and natural history of CeAD to provide the best care, it is also important for female patients to understand risk factors and presenting signs that should prompt evaluation for CeAD, particularly sex-predominant symptoms that have not traditionally been identified in the media as cause for urgent neurological evaluation, such as pain. Efforts to raise awareness regarding CeAD in females are paramount.

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