Pathophysiology and risk factors of cervical artery dissection: what have we learnt from large hospital-based cohorts?

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Purpose of review
Cervical artery dissection (CeAD) is a major cause of ischemic stroke in young and middle-aged adults, although relatively uncommon in the community. Recent large collaborative projects have provided new insights into mechanisms and risk factors of CeAD.

Recent findings
Pathologic changes observed at the media–adventitia border in temporal arteries of CeAD patients suggest a predisposing arterial wall weakness. In large multicenter series of CeAD patients, compared to age-matched healthy controls and patients with an ischemic stroke of another cause, hypertension and migraine, especially without aura, were confirmed as risk factors for CeAD, in addition to cervical trauma and recent infection. Hypercholesterolemia and being overweight were shown to be inversely associated with CeAD. Differences in risk factor profile and structural features between carotid and vertebral dissection suggest that their pathophysiology may partly differ. An association of CeAD with fibromuscular dysplasia and reversible cerebral vasoconstriction syndrome was described. Genetic risk factors of CeAD are still poorly understood.

Summary
Large cohorts of CeAD patients have refined our understanding of the pathophysiology and risk factors of CeAD, but the molecular mechanisms are still poorly understood. Ongoing high-throughput genetic projects will hopefully provide novel insight into the biological substrate of CeAD.

Keywords
cervical artery dissection, pathophysiology, risk factors, stroke

INTRODUCTION
Cervical artery dissection (CeAD) corresponds to a hematoma in the wall of an internal carotid or vertebral artery, and is a major cause of ischemic stroke in young and middle-aged adults [1–3]. The incidence of the disease is relatively low in the general population, estimated around 2.6–3/100,000 individuals per year [4,5]. The pathophysiology of CeAD is incompletely understood. Recently, data from large hospital-based cohorts of CeAD patients [6,7] have provided new insight into the risk factors and mechanisms of CeAD. In this review, we will primarily discuss arguments for an underlying arteriopathy, environmental risk factors and triggers, genetic predisposition, and the intriguing overlap with other vascular diseases. Prior to this, we propose a short overview of the clinical and radiological features, treatment and outcome of CeAD. Intracranial dissections are not discussed in this article.

SUMMARY OF CLINICAL AND RADIOLOGICAL FEATURES, TREATMENT AND OUTCOME OF CERVICAL ARTERY DISSECTION
The mean age of occurrence of CeAD is 44 years; although the disease can occur in children as well, it is very rare beyond age 65. Carotid dissections are more common than vertebral dissections, with a
CeAD patients often seem to have a predisposing arterial wall weakness, as suggested by various concomitant structural and functional arterial abnormalities described in association with CeAD, including pathologic changes in temporal arteries predominating at the media–adventitia border. CeAD is in most instances a multifactorial disease for which multiple environmental risk factors (cervical trauma, recent infection, hypertension, and migraine) and protective factors (hypercholesterolemia, overweight) have been described. Rarely, CeAD can occur as a complication of a rare inherited connective tissue disorder, mostly vascular Ehlers–Danlos syndrome; genetic variants modulating the risk of CeAD as part of a multifactorial predisposition are currently being explored in genome-wide association studies. An intriguing overlap of CeAD with other uncommon vascular disorders has been described, such as FMD and RCVS; exploring the molecular underpinnings of this overlap may provide useful insight into the pathophysiology of CeAD.

The rate of recurrent or de-novo cerebral ischemia after treatment initiation is low in CeAD patients (≤3% in the largest observational studies), with most events occurring in the first weeks following the diagnosis. Similarly, symptomatic CeAD recurrences are also rare and seem to be most frequent within the first months after the initial event (2.1% at 3 months in a series of 900 CeAD patients); some dissections that were diagnosed as multiple might have occurred sequentially within a short time frame. Some investigators consider early CeAD recurrences and multiple CeAD as the same entity. Late recurrences are possibly underestimated as studies with long-term follow up are scarce (a 7% rate was reported after 7.4 years of follow up in 200 patients) [1]. Mortality rates after CeAD are less than 4% in recently published cohorts. Functional outcome is usually good, approximately 75% of CeAD patients who suffered a stroke being independent at 3 months [1]. However, the psychological and social impact of CeAD can be substantial in these young, active individuals, and patients often complain of profound fatigue during the months following the event.
ARGUMENTS FOR UNDERLYING ARTERIAL WALL WEAKNESS

There is converging evidence suggesting that CeAD patients may have a predisposing arterial wall weakness (Fig. 2). Indeed, various concomitant structural and functional arterial abnormalities were described in association with CeAD, although mostly in small samples. These include larger aortic root diameter [20], increased stiffness of carotid wall material and circumferential wall stress [21], endothelial dysfunction [22], and arterial redundancies (kinks, coils, or loops) [23].

Pathological specimens of cervical arteries are difficult to obtain in CeAD patients, given low mortality rates and the fact that therapeutic approaches are largely based on medical treatment. As a surrogate pathological marker, superficial temporal arteries from 14 patients with spontaneous CeAD have been compared to those of nine accident victims without CeAD [24]. Pathologic changes predominating at the media–adventitia border, including vacuolar degeneration, capillary neoangiogenesis, and erythrocyte extravasation, were detected in all CeAD patients and only one control. These findings could suggest that CeAD patients have an underlying arteriopathy and that outer layers of the arterial wall may be primarily involved in the causation of the intramural hematoma.

Arterial dissection is a common feature of certain rare inherited connective tissue disorders, such as vascular Ehlers–Danlos syndrome, Marfan syndrome (MFS), or Loey–Dietz syndrome [25–27]. Hence, it has been hypothesized that CeAD patients may have an arterial wall weakness as part of some underlying connective tissue fragility. Skin biopsies performed in consecutive CeAD patients have shown that more than half of CeAD patients have ultrastructural skin connective tissue abnormalities on electron microscopy, the most common pattern being ‘Ehlers–Danlos type III like’
composite collagen fibrils and fragmentation of elastic fibers [28]. Skin biopsies performed in healthy relatives of three index CeAD patients have suggested that these connective tissue changes may be inherited according to an autosomal dominant pattern [29].

**ENVIRONMENTAL RISK FACTORS**

Cervical trauma is an important risk factor for CeAD [30,31]. Rarely, CeAD can occur after a major penetrating or blunt trauma. Often, CeAD patients report a minor cervical trauma in the days or weeks preceding the dissection. In a multicenter study on 966 CeAD patients from the Cervical Artery Dissections and Ischemic Stroke Patients (CADISP) consortium, cervical trauma in the previous month was reported in 40.5% of CeAD patients [32]. The trauma was minor, that is, not leading to a medical visit or hospitalization, in 88% of the cases. Prior cervical trauma was significantly more common in CeAD patients than in 651 patients who suffered an ischemic stroke of a cause other than CeAD (non-CeAD IS) or in 280 healthy controls. Among the numerous types of trauma that were reported, cervical manipulation therapy and cervical trauma during sports were more common in CeAD patients than in controls [32]. A causal relationship between minor cervical trauma and CeAD is often difficult to establish.

An association of CeAD with recent infection has been reported, potentially predisposing to CeAD via endothelial damage or prothrombotic mechanisms [33–35]. Acute CeAD is associated with high white blood cell counts compared with patients admitted for non-CeAD IS or with healthy controls [36], possibly reflecting a pre-existing inflammatory state. On cervical high-resolution MRI, patients with spontaneous CeAD more often have periarterial edema, often in conjunction with elevated C-reactive protein or erythrocyte sedimentation rate, than patients with traumatic CeAD, supporting the hypothesis of a predisposing role of inflammation in CeAD [37].

Until recently, data on the relationship of CeAD with vascular risk factors were controversial [1]. Associations had usually been examined in small samples, compared mostly with young patients with non-CeAD IS [21,23,33,34,38] and seldom healthy controls [39,40]. Within the CADISP consortium, the prevalence of vascular risk factors was compared between three groups of age-matched, sex-matched, and country-matched participants, of which there were 690 with CeAD, 556 with non-CeAD IS, and 1170 referents from the general population [41]. Compared with referents, CeAD patients were more
frequently hypertensive, and had a lower prevalence of hypercholesterolemia, obesity and overweight. An inverse association of CeAD with BMI was also shown in an independent large cohort [40]. All vascular risk factors were less frequent in CeAD patients compared to young patients with a non-CeAD IS. Elevated blood pressure could contribute to CeAD risk via increasing carotid stiffness [21]. The inverse association of CeAD with hypercholesterolemia and BMI, the young age of occurrence of CeAD, and the heterogeneous echostructure of carotid arteries in CeAD patients [21], all suggest that atherosclerosis is probably not a predisposing condition to CeAD, in contrast with aortic dissection [42]. With aging and arteriosclerosis, increased synthesis and reduced degradation of extracellular matrix components, as well as increasing collagen and elastin cross-links, could be hypothesized to make the arterial wall of cervical arteries more resistant to tears [43,44]. One could also speculate that lean persons have less adipose tissue protecting the arteries from minor cervical traumas. The association of CeAD with low cholesterol and BMI could also reflect shared genetic risk factors.

A seasonal pattern in the incidence of CeAD has been described, with a higher incidence in autumn and winter. Increased prevalence of infection and higher blood pressure levels in cold seasons have been proposed as putative underlying mechanisms [45*].

Migraine is a risk factor for CeAD [46,47]. In a systematic review and meta-analysis, migraine doubled the risk of CeAD [48]. Migraine is also a risk factor for ischemic stroke of other causes [49], but it is even more common in CeAD patients compared with age-matched and sex-matched patients with non-CeAD IS (36 vs. 27%) [50**]. Whereas migraine with aura is more strongly associated with ischemic stroke in general, migraine without aura is more commonly associated with CeAD. Frequency of stroke, dissection site (carotid or vertebral), clinical features, and outcome do not appear to differ between CeAD patients with and without migraine [50**]. The mechanisms underlying the association between CeAD and migraine are unclear. Vascular mechanisms are thought to play a key role in the pathophysiology of migraine [51]. A common predisposition to migraine and CeAD, for instance, via endothelial dysfunction [38,52] and shared genetic determinants, could be hypothesized.

Interestingly, although they largely overlap, the risk factor profile and structural features of CeAD are not identical for carotid and vertebral dissection, suggesting that their pathophysiology may partly differ [6]. Patients with carotid dissection are older and more often men. In carotid dissection, infections in the week preceding the dissection appear to be more common, whereas neck trauma in the previous month tends to be less often reported than in vertebral dissection. Aneurysmal dilatation is more common and bilateral dissection less frequent in patients with carotid dissection. The mechanisms underlying these differential features are speculative [6], but could include: anatomic features, such as anchoring of the vertebral artery to the cervical spine rendering it more vulnerable to mechanical solicitations, or closer proximity of carotid arteries to upper respiratory tract infections; different embryonic origins, pericytes and smooth muscle cells in carotid arteries being derived from the neural crest, whereas vertebral arteries emerge exclusively from the mesoderm [53]; partly distinct genetic susceptibility factors, supported by the high intrafamilial correlation for the affected vessels in familial CeAD [54].

GENETIC RISK FACTORS

CeAD is believed to be a multifactorial, complex disorder in the vast majority of cases. In rare instances, CeAD can occur as part of a monogenic disorder.

Monogenic forms of cervical artery dissection

Seldom, CeAD can occur as a complication of known, rare inherited connective tissue disorders, mostly vascular Ehlers–Danlos syndrome, probably in less than 2% of the cases according to large published series [25]. Vascular Ehlers–Danlos syndrome (vEDS) is a rare autosomal dominant disease, due to a mutation in the COL3A1 gene (prevalence: 0.2–1/100 000) [26]. The diagnosis is suggested clinically by the presence of arterial rupture, intestinal or uterine rupture, and family history of vEDS [55]. Other features include easy bruising, thin skin with visible veins, and characteristic facial features. In addition, the diagnosis must be confirmed by the demonstration of either a mutation in the COL3A1 gene or an abnormal type III procollagen synthesis. A positive diagnosis of vEDS has important implications, as vEDS patients are at increased risk of vessel rupture secondary to endovascular investigations or procedures, at high bleeding risk under anticoagulants, and celiprolol is recommended for the prevention of vascular complications [56].

The occurrence of CeAD in patients with MFS or other known inherited connective tissue disorders, such as Loeys–Dietz syndrome or osteogenesis imperfecta, seems even more rare than in patients with vEDS [25,27,57]. In MFS, CeAD may
occasionally occur as an extension of a proximal aortic dissection into the brachiocephalic arteries. Although there are a few individual reports of CeAD in MFS patients occurring independently of aortic lesions (<1% of CeAD patients in large series), information of the criteria used for the diagnosis of MFS is usually not available [25].

Familial cases of CeAD are rare (<2.5% in published series) and usually do not appear to occur in the context of a known inherited connective tissue disorder [58]. Linkage analyses have not identified any significant linkage peak to date, but their power was limited [57].

Although CeAD is sporadic in most cases, one cannot formally exclude that some patients suffer from a Mendelian disorder with incomplete penetrance, as could be suggested by the inherited abnormalities of skin connective tissue seen in otherwise healthy relatives of CeAD patients [29]. Systematic search for mutations in COL3A1 in a total of 53 CeAD patients [54,59–61], and in TGFBR1 and TGFBR2 in 56 consecutive CeAD patients [62], identified potentially deleterious mutations in three patients without any clinical evidence of vEDS or Loeys–Dietz syndrome.

Complex forms of cervical artery dissection
In most CeAD cases, there is no evidence for an underlying monogenic disease and CeAD seems to occur as part of a multifactorial predisposition. Heritability estimates of apparently sporadic CeAD are not available. In total, 18 genetic association studies testing the association of CeAD with candidate genetic variants have been published, on relatively small samples [57,63,64]. Of these, five have reported significant associations with three different candidate genes: ICAM-1 (rs5498) [65], COL3A1 (3′UTR 2-bp deletion) [61], and MTHFR (MTHFR-C677T) [66–68]. The first two were not replicated and a meta-analysis supports a modest association between the MTHFR-C677TT genotype and CeAD [57]. However, these studies have been markedly underpowered, mainly due to the low prevalence of CeAD that made it difficult to reach sufficient sample sizes. Moreover, candidate gene association studies are unable to identify novel genetic variants involved in unsuspected pathways, as they are based on what is already known or suspected about the pathophysiology of the disease [69]. A large, multicenter genome-wide association study (GWAS) of CeAD is currently underway, as part of the CADISP consortium [70]. GWAS consist of genotyping large numbers of genetic variants distributed across the chromosomes without requiring any a-priori hypothesis. This approach has recently been applied to a number of complex diseases, including stroke, with notable successes [71,72,73].

OVERLAP WITH OTHER VASCULAR DISEASES
Despite its low incidence, CeAD shows an intriguing correlation with other vascular or neurological diseases [74].

CeAD appears to be associated more often than predicted by chance with RCVS, a rare, underdiagnosed cause of severe headache [75]. This syndrome is characterized by segmental constriction of cerebral arteries resolving within 3 months, and may be revealed by recurrent thunderclap headaches, seizures, strokes, and nonaneurysmal subarachnoid hemorrhage [75]. Histological examination of brain arteries has been described as normal [75]. Putative triggers of RCVS include exposure to vasoactive drugs and the postpartum period [75]. In a recent series of 173 RCVS cases and 285 CeAD patients, 20 patients (12% of RCVS and 7% of CeAD patients) had both disorders [76]. CeAD patients with RCVS were more often women (90%) and more often had vertebral artery dissection than CeAD patients without RCVS (83 vs. approximately 30–40%) [76]. A history of migraine, mostly without aura, was highly prevalent in these patients (60 vs. 36% in CeAD patients with and without RCVS). Underlying mechanisms of RCVS are unknown and reasons for the phenotypic overlap with CeAD are elusive. Transient failure to regulate cerebral arterial tone, with sympathetic overactivity, has been suggested [77]. RCVS could be hypothesized to facilitate dissection by increasing pressure upstream of multiple intracranial stenoses, or by altering vessel wall vasa vasorum. Alternatively, CeAD could perhaps lead to the release of vasoactive substances triggering RCVS [75].

Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory vascular disease that affects primarily the renal and extracranial carotid and vertebral arteries, although other arterial beds can be involved [78,79]. Several histological subtypes exist, the most common being medial fibroplasia (80–90%), defined by alternating areas of thinned media and thickened collagen-containing medial ridges [80]. The vast majority of patients are women (~90%) with a mean age at diagnosis of approximately 52 years, and a high prevalence of hypertension [81]. The disease is often considered to be rare, but the prevalence of renal FMD was reported to be around 4% in kidney donors [82]. In the largest published registry, on 447 patients with FMD, 18.3% of the patients suffered from arterial dissection, the most common dissection site
being carotid arteries (13.0% of FMD patients) followed by renal arteries (3.6%), and vertebral arteries (3.4%). Multiple dissections were slightly more common than in large CeAD series (18.5 vs. 15%). The frequency of FMD in CeAD registries varies widely, ranging between 5.6% in a large recent multicenter series of 983 CeAD patients [83*], and 16.5% in an older single center series of 102 CeAD patients [84], or even 21% in one of the first CeAD series on 62 patients [85]. Of note, in the latter two series most patients were investigated with digital subtraction angiography (DSA) [84,85] vs. less than 4% of the patients in the former [83*], as DSA has now been replaced by less invasive methods for the diagnosis of CeAD, mainly magnetic resonance angiography (MRA) or computed tomography angiography (CTA). However, these methods, especially MRA, may be less sensitive for the diagnosis of FMD. One series also reported a higher rate of CeAD recurrence in patients with FMD, requiring confirmation in independent samples [84]. The cause of FMD remains unknown. Cigarette smoking and a history of hypertension are associated with the disease and a genetic predisposition is suspected [86,87]. The mechanisms underlying the association between CeAD and FMD are unclear. FMD could predispose to CeAD via the arterial wall weakening that it entails, but common risk factors, including genetic, could also contribute to the phenotypic overlap.

CONCLUSION

Collaborative projects enabling the analysis of large cohorts of patients have been helpful in recent years in improving our understanding of the pathophysiology and risk factors of CeAD, a major cause of ischemic stroke in young adults. However, the molecular mechanisms underlying this disease are still poorly understood. Ongoing collaborative and hypothesis-free genetic projects will hopefully provide novel insight into the biological substrate of CeAD. Refining the analysis of the phenotypic overlap between CeAD and other vascular and neurological disorders, and assessing the genetic overlap between these may provide additional useful insight into the pathophysiology of CeAD. Dissecting the mechanisms of CeAD is an essential step in order to optimize treatment and prevention strategies.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest


11. This study describes gender-specific differences in the characteristics of CeAD.


16. This is a progress report from the CADISS (Cervical Artery Dissection in Stroke Study), testing the feasibility of a large-scale randomized trial at the acute phase of CeAD, comparing antiplatelets to anticoagulation. Results from the nonrandomized arm are reported.


20. This observational study reports on the outcome of patients with CeAD treated or not with thrombolysis, using a propensity score approach.


This study compares the frequency of recent cervical trauma between patients with CeAD and two sets of controls and examines whether the characteristics of the dissection differ according to the presence of a recent trauma.

35. Genus J, Dong-Si T, Grau AP, Lichy C. Postural C-reactive protein levels are elevated in cervical artery dissection. Stroke 2005; 36:e42–e44.

In this article, the authors compare leucocyte counts in patients admitted at the acute phase of a CeAD or a stroke of another cause.


Here, the authors explore the potential mechanisms underlying the seasonal variability of CeAD.


This is the largest GWAS of ischemic stroke to date on over 12,000 patients, showing that most genetic risk variants for ischemic stroke are probably associated with individual subtypes, providing strong arguments for performing a GWAS of CeAD, a very well defined, important subtype of ischemic stroke in young and middle-aged adults.


In this elegant review, the authors discuss the phenotypic overlap between various nonatherosclerotic, large vessel, cerebrovascular arteriopathies, including CeAD.

This is a landmark review on the pathophysiology, risk factors, diagnosis and management of RCVS.

In this article, the authors describe the largest series of patients with both CeAD and RCVS.


83. Béjot Y, Aboa-Eboule C, Debette S, et al. Characteristics and outcomes of patients with multiple cervical artery dissection. Stroke 2013; in press. In this article, the authors compared the features of patients with multiple vs. single artery CeAD, and describe an increased frequency of FMD in the former.


