The Journal of Headache and Pain

REVIEW

Open Access

Headaches attributed to cranial and cervical artery dissections

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Abstract

Headache is a common neurological symptom, often leading to the investigation of secondary causes, including cerebrovascular conditions such as cranial and cervical artery dissection (CCAD). CCAD, a significant cause of stroke in younger adults, commonly presents with headache or neck pain, isolated or accompanied by neurological deficits, and may mimic primary headache disorders, complicating timely diagnosis. This review explores the role of headache in CCAD, specifically addressing headache as an initial presentation, its evolution post-dissection, and as a potential risk factor of CCAD. By synthesizing current evidence, the review aims to improve early detection and clinical management of CCAD in headache patients.

Keywords Headache, Neck pain, Migraine, Craniocervical artery dissection, Cervical artery dissection, Intracranial artery dissection

Background

Epidemiology

Headache is the most common reason for neurological consultations and a frequent cause of emergency department (ED) visits [1]. Although generally benign, approximatively 2–5% of cases in the ED setting are associated with potentially life-threatening secondary conditions [2–4], such as cerebrovascular disorders [5]. For instance, over a third of patients with a thunderclap onset of headache are estimated to have a secondary cause [6]. Once secondary causes are ruled out, it is important to diagnose primary headache using the criteria outlined in the 3rd edition of the International Classification of Headache Disorders [7].

Migraine affects approximatively 14,4% of the population, peaking between the ages of 35 and 39 [8]. Neck pain is reported by three-quarter of migraineurs, particularly in chronic migraine, contributing to significant disability [9] and complicating diagnosis.

Cranial and cervical artery dissection (CCAD) is a common cause of stroke in young and middle-aged adults, resulting from a hematoma in the arterial wall, either intracranially (intracranial artery dissection - IAD), or extracranially (extracranial or cervical artery dissection– CeAD). Specific features of CeAD and IAD are synthetized in Table 1 [10–13].

Although the estimated annual incidence of CeAD has been estimated around 2.6 to 3 cases per 100,000 individuals, the true incidence is likely underestimated due to underdiagnosis and underreporting, especially for dissections that are not associated with a clinical stroke. While many dissections occur spontaneously, they can also be precipitated by mechanical stress or trauma, including

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Table 1 Specific features of extracranial and intracranial artery dissection [10–13, 15]

	Extracranial / Cervical Artery Dissection (CeAD)	Intracranial Artery Dissection (IAD)
Common population	Individuals of European ancestry	Individuals of East-Asian ancestry
Estimated incidence	2.6 to 3 cases per 100,000 individuals	Limited epidemiological data available
Mean age of onset	44-45.8 years	Mid-fifties
Anatomopathology	Intima, internal elastic lamina, media, external elastic lamina, adventice	Well-developed internal elastic lamina, paucity of elastic fibres in the media, no external elastic lamina, little adventitial tissue
Preferential site	Anterior circulation > posterior	Posterior circulation (mostly V4) > anterior
Clinical and radiological presentation	- Isolated headache and/or neck pain - Headache with local signs (Horner's syndrome, cranial nerve palsy) - Cerebral ischemia (66–75% of cases)	- Subarachnoid hemorrhage (50–60% of cases) - Cerebral ischemia (30–78% of cases) - Isolated headache
Key Diagnostic Signs on cerebral imaging	Mural hematoma, double lumen, intimal flap, dissecting aneurysm, tapering stenosis, or occlusion	Similar signs, but often more difficult to visualize

relatively minor events such as coughing, chiropractic manipulation, or neck movements. Minor trauma in the weeks preceding a dissection is reported in about 40% of patients in published series [14].

Clinical presentation

CCAD is typically revealed by headache and/or neck pain [15–32], which can present with a wide range of clinical features, and may sometimes mimic primary headache disorders [33–43], complicating the timely recognition of dissection as the underlying cause. Headache can range from sudden, severe pain to more insidious onset [30], and may be totally isolated or accompanied by local signs such as Horner's syndrome [16, 24–26, 28, 29, 31, 32], lower cranial nerve palsy, or focal neurological deficits if an ischemic stroke, or more seldom a subarachnoid hemorrhage, is also present [15]. Approximatively two-thirds to three-quarters of patients with CeAD experience cerebral ischemia, with higher prevalence in vertebral (90%) than in carotid dissection (73%) (946 patients, OR 0,32 (0,21 – 0,49)) [15], though this may be overestimated as many CeAD without stroke are managed in other departments or not hospitalized. IAD can present as isolated headache, ischemic stroke in 30–78% of cases, or, subarachnoid hemorrhage in 50–60% of cases, with a more ominous outcome [13, 44].

Diagnosis

Diagnosis of CCAD relies on brain and cervical imaging, with magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) or computed tomography angiography (CTA) being the preferred methods. On MRI, unenhanced T1-weighted imaging with fat saturation technique is highly sensitive for detecting mural hematoma, which appears as a spontaneous hyperintensity and supports the diagnosis, also visible on CTA. Other pathognomonic signs include the presence of a double lumen, an intimal flap (more seldom), or a dissecting aneurysm. The dissection can also present as a long tapering stenosis or an occlusion, requiring the presence of one of the aforementioned associated signs to confirm the diagnosis. The diagnosis of IAD is trickier than that of CeAD, due to the smaller size of the arteries and dynamic changes in the vessel morphology, sometimes requiring several follow-up images to confirm the diagnosis [13]. MRI also allows the detection of potential parenchymal complications. It is important to note that a mural hematoma can be challenging to detect on MRI on days 1 or 2 after the dissection, as it can initially appear as hypointense. In such cases, angio-CT or doppler ultrasound can be useful alternatives for detecting the hematoma or other specific features [45].

Scope of the review

This review explores the intricate relationship between headache and CCAD, focusing on three key aspects: (1) headache as an initial presenting symptom, (2) the evolution of headache and/or migraine after dissection, and (3) the potential link between migraine and the risk of arterial dissection. By synthesizing current evidence, we present a comprehensive analysis of the role of headache in the clinical presentation, diagnosis, management, outcomes, and pathophysiology of CCAD. Our aim is to raise awareness, support clinicians in the early detection of CCAD to prevent complications, highlight unmet needs and guide future research on the complex interaction between headache and CCAD.

Methods

Two independent reviewers conducted a comprehensive search of the PubMed database, up to August 2024, using the following terms: ("headache," OR "cephalalgia," OR "migraine,") AND ("dissection," OR "carotid," OR "vertebral," OR "intracranial," OR "cervical," OR "extracranial," OR "artery"). The search was limited to articles in the English language published in the past 30 years. No additional filters (e.g., study design) were applied.

Titles and abstracts were screened for eligibility. Full-text articles were reviewed if they met the inclusion criteria, which encompassed original research, randomized controlled trials, systematic reviews, open label studies, retrospective studies, population-based studies and guidelines. Additional sources cited within the references of these articles were also examined. Preference was given to data from large series ($N>40$) to enhance reliability and generalizability, with case reports included only when larger datasets were unavailable. Discrepancies between the two reviewers were resolved through discussion.

Results

Headache and/or neck pain as a presenting symptom of dissection

Headache is the most frequent clinical manifestation of CCAD, reported in 40–91% of cases and serving as the initial symptom in 14–72% of patients [15–32] (Table 2), with differences reflecting variations in study populations, including the focus on intracranial or extracranial dissections, specific arteries, or multiple sites, which may introduce selection bias. Interestingly, and this may challenge the diagnosis, individuals with a history of migraine are at increased risk of developing a CCAD, especially

Table 2 Headache and neck pain as a presenting symptom of cranial and cervical artery dissection: Summary of large series findings

Study *Author* (year)	Sample Size *N*	Site of dissection	Headache *N* (%)	Headache at admission *N* (%)	Neck pain *N* (%)	Isolated pain *N* (%)	Unilateral pain *N* (%)	Associated sign (H, T, CNP, V) *N* (%)
Biousse et al. (1995) [25]	80	eICAD	NR	NR	NR	At admission 31 (39)	NR	At admission H 15 (19) T 7 (9)
Silbert et al. (1995) [26]	161	CCAD	110 (68)	100 (62)	47 (29)	NR	96 (87)	ICAD: H 56 (41) CNP 22 (16)
Sturzenegger et al. (1995) [16]	44	ICAD	40 (91)	30 (68)	16 (36)	2 (4,5)	39 (98)	H 21 (48) T 3 CNP 2
Dziewas el at (2003) [28]	126	CeAD	57 (45)	NR	73 (58)	NR	NR	ICAD: H 29 (37) T 7 (9)
Arnold et al. (2006) [17]	245	CeAD	NR	NR	NR	20 (8)	11 (55)	NR
Campos et al. (2007) [27]	54	CeAD	39 (72)	NR	14 (26)	NR	26 (67)	NR
Debette et al. (2011) [15]	982	CeAD eICAD eVAD	NR	405 (68) 207 (65)	231(39) 212 (66)	NR	NR	NR
Fukuhara et al. (2015) [19]	83	VAD	NR	60 (72)	33 (55)	NR	41 (68)	V 20 (24) T 4 (0,5)
Koboyashi et al. (2016) [21]	123	VAD	NR	69 (56)	eVAD 10 (100)	NR	NR	V 24 (20)
Giannini et al. (2017) [29]	77	CCAD	31 (40)	NR	25 (33)	NR	NR	H 26 (34)
Wang et al. (2019) [18]	81	CCAD with IS	NR	34 (42)	NR	7 (9)	(58)	NR
Gallerini et al. (2019) [24]	49	CeAD	28 (57)	NR	22 (45)	11 (22)	NR	H 5 (10) CNP 5 (10) V 2
Mayer et al. (2019) [31]	259	CeAD	205 (79)	NR	NR	NR	NR	H 42 (16) T 19 (7) CNP 13 (5)
Wang et al. (2019) [20]	146	CCAD	60 (41)	20 (14)	10 (7)	NR	(47)	NR
Vidale et al. (2020) [30]	419	CCAD	295 (70)	87 (36)	NR	NR	(72)	NR
Mayer-Suess et al. (2022) [32]	279	CeAD	220 (81)	207 (77)	145 (52)	NR	95 (44)	H 42 (16) T 19 (7) CNP 89 (41)
Hashimoto et al. (2023) [22]	93	CCAD with headache	NR	NR	NR	NR	59 (63)	NR
Lee et al. (2023) [23]	306	iVAD	NR	237 (64)	NR	126 (34)	124 (52)	NR
Total	3,607	-	1,085/1,614 (67)	1,456/2,624 (55)	-	-	-	-

CCAD: Cranial and cervical artery dissection; CeAD: Cervical artery dissection; eVAD: Extracranial vertebral artery dissection; eICAD: Extracranial internal carotid artery dissection; IS: Ischemic stroke; H: Horner's syndrome; T: Tinnitus; CNP: Cranial nerve palsy; V: Vertigo; NR: Not reported

CeAD (see Migraine as a risk factor for dissection), and also more likely to present with headache (941 patients, Odds-ratio (OR) 1,43 (1,05 – 1,93), adjusted $p = 0{,}023$) [46]. Headache is reported as unilateral in 44–98% of cases (Table 2), most often occurring ipsilaterally to the dissection site (16–23, 26–27, 30, 32). It is frequently described as throbbing or pulsatile in nature [18–20, 26, 27, 30, 32]. Severe intensity is reported in 55% of cases, according to a review of 419 patients [30]. The characteristics of these headaches can vary based on the affected artery, location of the dissection, and associated complications. For instance, headache is predominantly frontal or temporal in carotid dissections (41–64%) [16, 18, 26, 27, 30] and more frequently occipital or nuchal in vertebral artery dissections (47-76.5%) [18, 21, 26–30]. Associated neck pain is also common, reported with various frequencies [15, 16, 19–21, 24, 26–29, 32] (Table 2). It is reported as significantly more prevalent in extracranial vertebral dissections versus carotid dissections (982 patients, OR 0,36 (0,27 – 0,48), $p < 0{,}0001$) [15] and in cases of multiple or early recurrent dissections (1958 patients, OR 1,36 (1,01–1,84)) [47]. In intracranial dissections, headache has been reported in as many as 80% of cases, with sudden and intense onset in 13–17% of patients [13]. Headache was reported as different from any previous known pain, and requiring analgesics. Moreover, headache characteristics can evolve with time, potentially complicating early recognition and diagnosis. The International Classification of Headache Disorders has outlined diagnostic criteria for headaches attributed to cervical artery dissection (Table 3) [7].

Table 3 ICHD-3 diagnostic criteria for acute headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection [7]

Diagnostic criteria:
A. Any new headache and/or facial or neck pain fulfilling criteria A B C D E
B. Cervical carotid or vertebral dissection has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
1. pain has developed in close temporal relation to other local signs of the cervical artery dissection, or has led to its diagnosis
2. either or both of the following:
• a) pain has significantly worsened in parallel with other signs of the cervical artery dissection
• b) pain has significantly improved or resolved within 1 month of its onset
3. either or both of the following:
• a) pain is severe and continuous for days or longer
• b) pain precedes signs of acute retinal and/or cerebral ischaemia
4. pain is unilateral and ipsilateral to the affected cervical artery
D. Either of the following:
1. headache has resolved within 3 months
2. headache has not yet resolved but 3 months have not yet passed
E. Not better accounted for by another ICHD-3 diagnosis.

Headache and/or neck pain can sometimes be the only presenting symptom of a dissection (4,5–34% of cases) (16–18, 23–24, 48–49) (Table 2). The historical term 'carotidynia', once used to describe idiopathic pain and tenderness over the carotid artery, has evolved with advances in cerebral imaging, revealing that, in some cases, an underlying arterial dissection may actually be the cause of this symptom [49]. The term 'carotidynia' has further evolved into a more precise and recognized entity known as transient perivascular inflammation of the carotid artery (TIPIC). TIPIC refers to a temporary inflammation around the carotid bifurcation, is associated with a favorable prognosis, and should be considered a differential diagnosis of CeAD [50]. In a large series of 247 CeAD patients, approximately 8% presented with headache and/or neck pain as the sole symptom [17], with most cases involving extracranial vertebral dissection. Isolated headache might be more common in IAD, though specific data are limited [13, 44]. This highlights the importance of considering dissection in patients with an isolated unusual headache and who have no prior history of similar symptoms. Additionally, in the CeAD series, the median delay from symptom onset to diagnosis was 7 days, with intervals extending up to 29 days, underscoring the challenge of recognizing dissection early and the need to consider it in front of an unusual headache to prevent complications [17]. Dissection should be particularly suspected if headache and/or neck pain is unilateral ($p = 0{,}04$) [19], though bilateral presentations should not rule it out (Table 2).

In the absence of associated cerebral (or retinal) ischemia, dissection diagnosis may be further supported by the presence of associated "local" signs such as partial or complete Horner syndrome, which occurs in 10–48% of patients with carotid dissections due to compression of the sympathetic nerve [16, 24–26, 28, 29, 31, 32], cranial nerve palsy (especially the lower cranial nerves), and tinnitus, which is reported in 3–9% of these patients [16, 19, 25, 28, 31, 32] (Table 2). In vertebral artery dissections, associated symptoms such as nausea and vomiting are noted in 20–33% of cases [18, 22] and the presence of vertigo raises the probability of detecting vertebral dissection, though studies do not specify the presence or absence of parenchymal lesion, particularly in the posterior region [19].

Importantly, CCAD may present with headache patterns that mimic primary headache disorders, potentially leading to diagnostic delays and subsequent complications. Cases have been reported where dissections initially manifested as primary headache syndromes, including cluster headaches [33–35], hemicrania continua [36, 37], or migraine with or without aura [38–42, 51]. In a review of 77 cases, dissection was identified as the third most common cause of secondary cluster

headache, accounting for 14,3% of cases, with nearly all cases involving extracranial internal carotid artery localization [43]. Thus, physicians should consider ruling out dissection when faced with a first episode of cluster headache or when atypical features are present. These atypical features include abnormal neurological exams, persistent headache between attacks, persistent Horner's syndrome between attacks, unusual attack frequency, or resistance to standard treatment. In such cases, imaging should be performed to investigate potential secondary causes. Dissection has also been reported to present with symptoms that mimic migraine with aura, including transient, and progressive positive neurological symptoms - often visual or sensory -, that may or may not be followed by headache, and are not necessary linked to ischemic stroke. This can also occur in patients who either have no prior history of migraine or have a history of migraine without aura [38–41]. These observations emphasize the importance of investigating a first occurrence of atypical aura with specific imaging. This is supported by a mouse model study, which demonstrated that injecting air microemboli can induce cortical spreading depression without causing infarction, suggesting that microembolism– and resultant hypoperfusion - could be underlying mechanisms in CCAD presenting as aura [52]. Finally, as mentioned earlier, minor trauma can precede CCAD, but it can also be a confounding factor, delaying the diagnosis in favor of a post-traumatic headache. All these masquerading presentations can obscure the underlying vascular pathology, particularly in patients who may have pre-existing headache disorders. This emphasizes the fact that any new-onset primary headache disorder and/or pattern modification of a pre-existing one must be explored with attention.

Unfortunately, there is no specific data on the management of pain in CCAD. However, a notable finding from a retrospective study of 197 patients is the high resistance to self-administered analgesia prior to consultation, reported in 86% of CCAD patients compared to 48% of non-CCAD patients with unusual headache, suggesting that non-response to usual analgesics may be an additional argument for CCAD in cases of unusual headache (OR 5,3 (1,95 – 14,6), $p = 0{,}001$) [22].

Table 4 Persistent headache following cranial and cervical artery dissection: Summary of study findings

Study *Author* (year)	Sample Size *N*	Site of dissection	Duration of follow-up	Persistent headache *N* (%)
Leys et al. (1995) [55]	105	CeAD	36 months	21 (5)
Schytz et al. (2014) [54]	19	CeAD	6 months	5 (29)
Martins et al. (2023) [53]	92	CCAD	≥ 3 months, 2,5 years	24 (26), 20 (22)

CCAD: Cranial and cervical artery dissection; CeAD: Cervical artery dissection

Headache course after dissection

Following the initial headache present at the acute stage of dissection, this section will focus on the progression of headaches beyond the acute phase. We will examine two aspects: first, the persistence of post-dissection headaches in a significant proportion of patients even after the vascular injury has resolved; and second, the impact on individuals with a pre-existing history of primary headaches who may experience modifications in headache patterns or severity after the dissection.

Persistent post-dissection headaches

Persistent headaches following CCAD have not been extensively documented in the literature, yet they represent a significant clinical challenge. Most available evidence focuses on CeAD, with limited data on post-dissection headache specific to IAD. These headaches can persist for weeks, months, or even years after the initial vascular injury, potentially impairing both quality of life and long-term clinical recovery. Reported frequencies of persistent headache vary, with studies showing that approximately one-quarter of patients experience them at least three [53] to six months post-dissection [54], and around 19% still suffer from headaches 36 months after the event [55] (Table 4).

Martins et al. [53] studied the characteristics and contributors to the persistence of headache in 92 patients. They found that in 68% of cases, the persistent pain closely resembled the headache that initially signaled the dissection. Typically, these headaches were described as throbbing, of moderate intensity, and predominantly located in the nuchal/cervical or holocranial regions. In some patients, the headache pattern remained largely unchanged apart from variations in frequency. In others, the headache evolved to resemble more common primary headache disorders such as migraine or tension-type headaches, with 20% of patients reporting daily headaches. Photophobia was the most common accompanying symptom, present in 20% of cases.

Several risk factors for developing persistent post-dissection headaches have been identified, including a previous history of headaches (OR 59,8, $p < 0{,}001$)– particularly migraine without aura -, presence of headache and/or neck pain at admission (OR 25,4, $p = 0{,}005$), involvement of the posterior circulation (OR 7,6, $p < 0{,}001$), and lower National Institutes of Health Stroke Scale (NIHSS) scores for patients with associated stroke (OR 5, $p = 0{,}025$) [53]. The underlying pathophysiology remains unclear, but it is thought to involve ongoing inflammatory processes at the site of the dissection that may lead to prolonged sensitization of nearby pain

Table 5 Evolution of pre-existing primary headache in cranial and cervical artery dissection: Summary of study findings

Study *Author* (year)	Sample Size *N*	Site of dissection	Previous history of PH / migraine *N* (%)	Duration of follow-up	Previous headache improvement following dissection *N* (%)
Campos et al. (2007) [27]	54	CeAD	PH 35 (65)	32 months	26 (74)
Artto et al. (2010) [61]	626	313 CeAD vs. 313 controls in migraineurs	Migraine 626 (100)	3,5 years	29/57 (51)
Censori et al. (2013) [62]	43	IS in migraineurs including 11 CCAD	Migraine 43 (100)	6 months, 1 year	11/11 (100) 11/11 (100)
De Giuli et al. (2019) [63]	174	87 CeAD IS vs. 87 non-CeAD IS in migraineurs	Migraine 174 (100)	36 months	53 (61) in CeAD vs. 38 (44) in non-CeAD ($p = 0{,}023$)

CeAD: Cervical artery dissection; CCAD: Cranial and cervical artery dissection; IS: Ischemic stroke; PH: Primary headache

pathways. Additionally, dissection-related alterations in the cervical and cranial nerves are suspected to result in long-term hypersensitivity, contributing to the persistence of pain [53, 56, 57]. Evidence-based treatment is lacking. Rest and analgesics seemed to improve the symptoms in most of the patients of this one retrospective cohort study (92 patients, 55%) [53]. In clinical practice, persistent headaches could be managed according to the primary headache phenotype they present. For example, headaches with migraine-like features could be treated using anti-migraine therapies. Anti-inflammatory treatments, including nonsteroidal anti-inflammatory drugs (NSAIDs), may be considered if inflammation is suspected to play a role in headache's pathophysiology.

Finally, while depression has been related to persistent headaches following stroke in general [58–60], risk factors of persistent headaches after CCAD specifically have not been extensively studied. Nonetheless, psychosocial factors are hypothesized to play a significant role [35], both as risk factors for the development of chronic headaches and as factors that amplify headache severity, creating a complex interplay between physical and mental health.

Evolution of pre-existing primary headaches

Pre-existing primary headache disorders, particularly migraine, are frequently observed in patients with CCAD, and the progression of these headaches can be influenced by the vascular event. Intriguingly, small case series have reported a significant migraine and primary headache improvement [27, 61, 62] following CCAD (Table 5). In a prospective case-control study by De Giuli et al. [63], focusing on 174 migraineurs with ischemic stroke related to CeAD versus other causes of stroke, migraine resolution occurred in 14% of cases in the CeAD group (versus 0% in the non-CeAD group, $p \leq 0{,}001$). Additionally, over 60% of patients in the CeAD group reported migraine improvement during a median follow-up of 36 months (Table 5). Reductions in migraine frequency ($p = 0{,}001$), pain intensity ($p \leq 0{,}001$), and medication use ($p = 0{,}007$) were observed. Predictors of migraine improvement post-dissection included advanced age (age > 39; OR 3,31 (1,16 – 9,41), $p = 0{,}025$), higher baseline migraine frequency (> 1 attacks/month, OR 3,5 (1,19 – 10,28), $p = 0{,}022$), and higher pain intensity (pain scale > 5, OR 4 (1,24 – 12,87), $p = 0{,}020$).

Potential confounding factors are suggested to contribute to these changes including the natural reduction in migraine frequency with age, the effects of aspirin therapy following dissection, and lifestyle or psychological changes after the dissection. However, biological mechanisms common to both dissection and migraine are also hypothesized to play a role. These remain speculative but may involve vascular remodeling after dissection, which could modify vascular responses to migraine triggers. Alternatively, dissection may influence neural pathways involved in migraine pathophysiology, recalibrating pain thresholds and decreasing migraine susceptibility [64]. However, the variability in patient outcomes suggests that individual differences in vascular and neural responses significantly influence the extent of headache improvement.

Management of migraine attacks after CCAD can be challenging as triptans are contraindicated in patients with a history of transient ischemic attack, stroke or uncontrolled vascular risk factor. Additionally, the use of NSAIDs is limited when long-term aspirin therapy is needed. In such cases, gepans and ditans offer a reasonable alternative for the acute treatment of migraine attacks [5, 65–70]. Therefore, this recommendation is based on their mechanisms of action and expert opinion, rather than established literature. A more frequent use of prophylactic treatments to reduce the frequency of acute attacks may also be suggested in those situations.

Migraine as a risk factor for dissection

This section will explore the potential link between migraine and CCAD. Initially suggested by

epidemiological data and more recently supported by genetic evidence, a causal relationship between migraine and increased risk of dissection is emerging. Understanding these associations may provide insights into the pathophysiology of dissection and its relationship to primary headache disorders.

Migraine is a frequent neurological disorder, with an estimated global prevalence of 14,4% [8]. While its pathophysiology remains complex and incompletely understood, vascular mechanisms are believed to contribute to its manifestation [71]. The link between migraine and CeAD has been extensively investigated, with some researchers suggesting it may partly explain the association between migraine and stroke, particularly in young adults. A significant correlation between migraine and CeAD was initially shown in a French case-control study, independent of migraine subtype (50 patients, X^2 4,1, $p < 0,05$) [72]. Rist et al. [51] conducted a meta-analysis of 5 studies, revealing that migraine doubles the risk of CeAD (OR 2,06 (1,33 – 3,19)), this association being significant for migraine without aura only (OR 1,94 (1,21 – 3,1)), while it might be related to the relatively small number of aura patients. A second meta-analysis supported this, showing a significant association between CeAD and migraine (9857 patients, OR 1,74 (1,38 – 2,19)), and specifically migraine without aura (OR 1,86 (1,55 – 2,24)) [73].

The Cervical Artery Dissection Ischemic Stroke Patients (CADISP) study [46], which included over 1,600 patients, further explored this association. It found that migraine was more prevalent among patients with CeAD compared to age-matched patients with strokes of other etiologies (35.7 vs. 27.4%, OR 1,51 (1,15 – 1,99), $p = 0,003$), again particularly migraine without aura (OR 2,09 (1,46 – 2,99), $p < 0,001$). Additionally, migraineurs more frequently presented with headache at the acute onset of dissection (73,7 vs. 63,2%, OR 1,43 (1,05 – 1,93), $p = 0,023$). However, migraine did not influence stroke risk in CeAD patients or the prognosis of CeAD [46].

The mechanisms underlying this association remain unclear but may involve, at least partly, endothelial dysfunction, altered systemic vascular reactivity, and shared genetic susceptibility [51]. Daghals et al. [74] investigated shared genetic variation between migraine, stroke, and CeAD. By analyzing genome-wide association studies (GWAS) data for migraine and CeAD, they identified several genetic loci shared between these conditions, including *ADAMTSL4/ECM1*, *PLCE1*, *MRVI1*, *FHL5*, *PHACTR1/EDN1*, and *LRP1*, suggesting common pathways related to vascular development and function. Most prominently, a common genetic variant on chromosome 6 was identified as being associated with risk of both migraine (OR 0,86 (0,81 – 0,91), $p = 3,20 \times 10^{-8}$) [75] and CeAD (1 393 CeAD vs. controls, OR 0,75 (0,69 – 0,82), $p = 4,46 \times 10^{-10}$) [76], in the same direction. This locus appears to be highly pleiotropic, being also associated with risk of fibromuscular dysplasia and coronary artery dissection in the same direction, and of coronary artery disease and calcification in the opposite direction [77, 78]. The causal gene in this region (*PHACTR1* or *EDN1*) is still a subject of controversy [77, 79–81]. Another area of interest concerned the increased activity of matrix metalloproteinases (MMPs), proteolytic enzymes that regulate extracellular matrix homeostasis, which has been found in both migraine [82, 83] (respectively 145 patients, $p < 0,005$ and 44 patients, $p < 0,001$) and CeAD (99 patients, $p = 0,11$) [84]. The hypothesis is that chronically elevated MMP levels in migraine sufferers could weaken the arterial wall, making them more susceptible to CeAD following minor traumatisms [85].

Fibromuscular dysplasia (FMD), a nonatherosclerotic, noninflammatory vascular disease affecting medium-sized arteries, has also been linked to CeAD. In a large cohort of 1,283 patients with spontaneous CeAD, 8% were diagnosed with cerebrovascular FMD (cFMD). History of migraine and presence of intracranial aneurysms were significantly associated with the presence of cFMD (respectively OR 1,78 (1,13 – 2,79), $p = 0,01$ and OR 8,71 (4,06–18,68), $p \leq 0,001$). Moreover, migraine and cFMD were both predictive of recurrent dissection (respectively OR 2,07 (1,06 – 4,03), $p = 0,033$ and OR 3,4 (1,58 – 7,31), $p = 0,002$), suggesting, again, an underlying pattern of migraine and dissection conditions [86]. Interestingly, the PHACTR1 gene polymorphism rs9349379, previously linked to migraine and CeAD, has also been reported as a risk allele for FMD (5 049 individuals, OR 1,39 (1,25 – 1,54, $p = 7,36 \times 10^{-10}$) [87].

Finally, hypertension has been identified as a risk factor for CeAD (690 CeAD and 556 controls, OR 1,67 (1,32 – 2,1), $p < 0,0001$) [88], with evidence supporting a causal association between higher blood pressure and increased CeAD risk (systolic blood pressure (SBP): OR 1,51 (1,32 – 1,72), diastolic blood pressure (DBP): OR 2,4 (1,92 – 3), $p < 0,0001$) and multiple or early recurrence (SBP: OR 1,2 (0,98 – 1,48), $p = 0,0799$; DBP: OR 1,38 (1,12 – 1,71), $p < 0,0029$) [89]. This association is thought to be partially related to the existence of FMD [89] which is also a rare cause of hypertension. Moreover, hypertension can present with headache, including migraine, although this relationship remains controversial [90]. This complicates the clinical picture but underscores the complex interrelationship between these conditions.

Despite significant advancements, the pathophysiology linking migraine and CCAD remains incompletely understood. As brain imaging techniques continue to improve in resolution, one hypothesis is that future technologies will allow for the detection of subtle abnormalities that are currently undetectable with 2024 imaging

modalities (e.g. micro-dissection or endothelial damage, although this is speculative). Another area of research is the exploration of related diseases that may co-occur or share underlying mechanisms, such as reversible cerebral vasoconstriction syndrome (RCVS) [85] or other forms of arterial dissection, such as spontaneous coronary artery dissection (SCAD) [91]. RCVS shares several characteristics with both migraine and CeAD and has been proposed as part of a continuum of vascular disorders associated with both pathologies [85]. Similarly, the prevalence of migraine in SCAD, as reported in the iSCAD Registry cohort, highlights a potential overlap in the vascular biology of these conditions [91]. Investigating these related conditions further may provide new insights into shared mechanisms and help generate novel hypotheses for future research.

Conclusion

This review highlights the multifaceted role of headache in CCAD, emphasizing its importance not only as a common presenting or associated symptom but also as a persistent and impactful consequence. Headache at the acute onset of dissection is highly variable; it may be isolated and sometimes mimic primary headache disorders, significantly complicating diagnosis. This variability underscores the need for prompt and thorough investigation of any new or unusual headache, neck pain, or change in the pattern of a pre-existing primary headache.

Persistent headache following CCAD affects approximately a quarter of patients, often persisting for months or years, significantly influencing recovery and quality of life. Paradoxically, individuals with pre-existing primary headaches, such as migraine, may experience an improvement in their underlying disorder after the event, reflecting the complex interplay between vascular events and headache disorders. Emerging evidence of shared genetic and biological factors– such as endothelial dysfunction and specific gene variants - between migraine and CCAD points to common mechanisms, offering important avenues for future research.

Despite advances in understanding these connections, substantial unmet needs persist, particularly regarding the effective management of post-dissection headache. Current data on pain management remain insufficient, leaving patients with limited guidance on relief options. Addressing these gaps through targeted research and clinical strategies is essential to improving outcomes for CCAD patients.

Abbreviations

CADISP	Cervical Artery Dissection Ischemic Stroke Patients
CCAD	Cervicocerebral artery dissection
CeAD	Cervical artery dissection
cFMD	Cerebrovascular fibromuscular dysplasia
CTA	Computed tomography angiography
DBP	Diastolic blood pressure
FMD	Fibromuscular dysplasia
IAD	Intracranial artery dissection
GAWS	Genome-wide association studies
MMP	Matrix metalloproteinases
MRA	Magnetic resonance Angiography
MRI	Magnetic resonance Imagery
MTHFR	Methylenetetrahydrofolate reductase
NIHSS	National Institutes of Health Stroke Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds-Ratio
RCVS	Reversible cerebral vasoconstriction syndrome
SBP	Systolic blood pressure
SCAD	Spontaneous coronary artery dissection
TGFb	Transforming growth factor beta

Acknowledgements

Not applicable.

Author contributions

JM directed the project. DD and JM performed the systematic search. DD wrote the initial manuscript. JM and SB reviewed the manuscript. All authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

DD has no competing interests; SB has no competing interests; JM has received financial supports for boards and meeting presentations from Lilly, Abbvie, TEVA, Lundbeck, Pfizer and Orion Pharma. He has received travel fees for congress from Ipsen Pharmaceuticals, Abbvie, Lundbeck, SOS Oxygen and Dr Reddy's.

Received: 3 December 2024 / Accepted: 21 January 2025
Published online: 06 February 2025

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