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Review Article

The Link Between Migraine, Reversible Cerebral Vasoconstriction Syndrome and Cervical Artery Dissection

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Headache is the common thread of migraine, reversible cerebral vasoconstriction syndrome (RCVS) and cervical artery dissection (CeAD), three medical conditions that otherwise appear to be very different. However, epidemiological, clinical and genetic data suggest that these conditions share common and complex features and are, at least partly, linked. The purpose of this manuscript is to review existing evidence for an association between migraine, RCVS and CeAD and discuss the potential underlying mechanisms.

Key words: migraine, reversible cerebral vasoconstriction syndrome, cervical artery dissection, headache, cerebrovascular disease

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INTRODUCTION

Migraine, reversible cerebral vasoconstriction syndrome (RCVS) and cervical artery dissection (CeAD) are three medical conditions that appear to be very different but share headache as common thread. Migraine is the most disabling primary headache disorder,[1] whereas RCVS and CeAD are acute neurovascular disorders that can cause secondary headaches and stroke. The higher frequency of migraine among patients with CeAD as well as the occurrence of migraine attacks symptomatic of RCVS and CeAD suggest that these entities are partly linked.

Migraine affects 15% of the general population, with prevalence peaks in the young and around 50 years of age.[2] This primary headache disorder is characterized by recurrent attacks of headache

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associated with autonomic, gastro-intestinal and/or neurological symptoms (aura).[3] Beyond the disability related to headaches[1] and the slight increase in stroke risk among migraineurs with aura,[4] migraine remains a benign disease.

Cervical artery dissection is an acute arterial disease characterized by a hematoma in the wall of the internal carotid or vertebral artery. It is an uncommon but likely underestimated disorder, with an incidence of 3/100,000 inhabitants per year. Its most frequent clinical presentation is cervical pain and headache, which is often (67-77%) associated with, and often precedes, brain and retinal ischemic manifestations; CeAD represents a major cause of ischemic stroke in young and middle-aged adults.[5] Less frequent clinical presentations include Horner syndrome, tinnitus, cranial nerve palsy, and, when the dissection involves intracerebral arteries, subarachnoid hemorrhage. The pathophysiology is incompletely understood. In most instances, CeAD is believed to be a multifactorial disease, with an underlying arterial wall weakness, possibly partly determined by genetic factors.[5,6] Risk factors of CeAD include cervical trauma (often minor, the causal relationship being sometimes difficult to establish), recent infection, hypertension, migraine, certain anatomical characteristics (eg, short distance beyond styloid and carotid artery),[7] while BMI and hypercholesterolemia are inversely associated with CeAD risk.[8] CeAD is also more often seen in patients with fibromuscular dysplasia, another nonatherosclerotic arteriopathy.[5]

Reversible cerebral vasoconstriction syndrome is a rare, but increasingly recognized clinical-radiological syndrome characterized by severe acute headaches and multifocal constrictions of cerebral arteries resolving spontaneously within 3 months.[9–11] The clinical hallmark of the syndrome is severe, often thunderclap and recurrent headache that may be isolated or associated with seizures and transient or persistent focal deficits. Brain imaging may be normal or reveal cortical subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke and/or posterior reversible encephalopathy syndrome.[12–14] RCVS mainly affects young and middle-aged adults with a strong female preponderance (69-90%) and usually occurs in peculiar settings such as postpartum and exposure to cannabis, sympathomimetic, or serotoninergic substances. The prevailing hypothesis for the underlying mechanism is a transient disturbance of the regulation of cerebral arterial tone.[10]

One major difference between migraine, CeAD and RCVS is that the diagnosis of migraine remains entirely clinical whereas that of CeAD and RCVS relies on both clinical symptoms and neuroimaging. Diagnosis of CeAD and RCVS may be a challenge in patients presenting with isolated headache. In migraineurs, a new-onset headache symptomatic of CeAD and/or RCVS may be misdiagnosed as a severe migraine attack. Moreover, CeAD and RCVS can manifest as mild unspecific headaches, or as attacks of secondary migraine with aura, which are clinically indistinguishable from attacks of primary migraine.

Although these three conditions appear different regarding clinical presentation, prevalence, prognosis and underlying mechanisms, there is mounting evidence suggesting that they are, at least partly, linked. The purpose of this manuscript is to review existing evidence for an association between migraine, CeAD and RCVS and discuss the potential underlying mechanisms.

METHODS

We searched PubMed (in English) up to August 2015 for relevant articles with the following search terms "reversible cerebral vasoconstriction syndrome AND dissection," "migraine AND dissection," "reversible cerebral vasoconstriction syndrome AND migraine." A narrative review has been performed with these articles as well as others identified in the bibliography of these articles. When meta-analyses and/or large series were available, smaller series or isolated case reports have been omitted.

To improve the readability of this manuscript, we present the links between migraine, RCVS and CeAD by presenting two by two associations and discuss in the text the potential link with the third one. When available, details on whether one disease influences the other are given.

MIGRAINE AND CeAD

We discuss the increased risk of CeAD among migraineurs,[15,16] the fact that migraine attacks may reveal CeAD[17] and the fact that the occurrence of a CeAD may modify the clinical presentation of migraine.[18,19]

Epidemiological Evidence for an Increased Risk of CeAD in Migraine.—A large meta-analysis gathering 5 case-control studies investigating the association between migraine and CeAD showed that being a migraineur doubled the risk of CeAD (Odds Ratio [OR] 2.01, 95% CI 1.33-3.19), without clear evidence for a difference according to aura status or gender.[16] Likewise, a recent large international case-control study (CADISP, Cervical Artery Dissection and Ischemic Stroke Patients) including more than 1600 subjects confirmed the increased risk of CeAD among migraineurs (OR 1.51, 95% CI 1.15-1.99).[15] Migraine, especially with aura, is also a risk factor for ischemic stroke, regardless of the underlying mechanism.[20] However, the CADISP study suggested first that migraine was more common among stroke patients with CeAD compared to age-and gender-matched stroke patients without CeAD and second that the association with CeAD was mostly seen for migraine without aura.[15] Interestingly, among patients with CeAD, being a migraineur had no influence on the occurrence of cerebral infarction, on the type (vertebral or carotid CeAD) or the number of dissected vessels, on the vessel patency, on the clinical outcome or on the occurrence of complications.[15] At the acute stage, headache was more frequent in migraineurs (73.7% vs 63.2%),[15] in agreement with prior series,[21] although this has been debated in some smaller cohorts.[15,21–23] Of note, a case series of patients with CeAD suggested that migraine with aura was associated with aneurysmal form of dissection but the small number of patients and the lack of multivariate analysis preclude firm conclusions.[24]

Potential Mechanisms Underlying the Increased Risk of CeAD in Migraine.—The underlying mechanisms of the increased risk of CeAD among migraineurs remain unknown. A recent genome-wide association study of CeAD has identified a genetic variant on chromosome 6, in the *PHACTR1* gene, which is associated with a reduced risk of CeAD.[25] Interestingly, the same allele was also identified by genome-wide association studies to be associated with a reduced risk of migraine.[26] The mechanism by which *PHACTR1* reduces the risk of migraine and CeAD is unclear. *PHACTR1* is in a highly conserved genomic region, suggesting a crucial involvement in biological processes[27] but its function is poorly understood. Experimental studies revealed a pivotal role in vascular tube formation and actin polymerization, suggesting a possible role in angiogenic processes.[28,29] Additional suggestive genetic risk loci for CeAD were also associated with migraine, especially without aura (*LRP1, FHL5*). These are strong arguments for shared biological pathways underlying CeAD and migraine. Remarkably, while shared genetic variation was also recently shown between migraine and ischemic stroke, none of the genome-wide risk loci for migraine and ischemic stroke overlap and only one genome-wide locus for larger artery stroke, in the chromosome 9p21 region, showed nominal association with migraine.[30]

Another hypothesis relies on transforming growth factor beta (TGFβ) pathway, which may also be involved, as suggested by the increased CSF[31] or serum[32,33] level of TGFβ 1 levels in migraineurs, by a large genome-wide association study in migraine that identified a locus near *TGFB2R* to be associated with migraine without aura[26] and by the involvement of TGFβ in Marfan or Loeys-Dietz syndrome,[34,35] two autosomal dominant connective tissue disorders characterized by large artery aneurysms or dissections, in which migraine is more frequent than in the general population.[36–42]

Based on biomarker studies and candidate gene approaches, a shared involvement of matrix metalloproteinases (MMP) and the methylenetetrahydrofolatereductase (MTHFR) metabolism in both migraine and CeAD has also been suggested.

An increased level or activity of MMP, proteolytic enzymes involved in the homeostasis of the extracellular matrix, has been shown both in CeAD[43] and in migraine.[44–47] This raises the hypothesis that chronic (ie, ictal and interictal) elevation of MMP levels in migraineurs may weaken the arterial wall to predispose to CeAD on mild

traumatic insults. However, whether migraine attacks induce an increase in MMP levels in all migraineurs, and whether these increased levels directly weaken the arterial wall, which predisposes to CeAD, remains to be proven. Interestingly, a genome-wide association study in migraine has identified a genetic variant associated with migraine vulnerability implicated in MMP pathways (rs 10504861, near MMP 16).[48] However, up to now, no genetic risk locus related to MMP pathway has been found in CeAD.[25]

Another hypothesis to explain the increased risk of CeAD among migraineurs relies on the MTHFR gene polymorphism, which plays a role in homocysteine metabolism and may be involved in endothelial dysfunction.[49] However, although candidate gene association studies suggested an association of the MTHFR 677CT polymorphism with the risk of CeAD[50,51] and migraine,[52–54] recent genome-wide association studies of CeAD[5] and migraine[26,48,55] on much larger samples did not confirm this association.

Clinical Evidence for Secondary Migraine Attacks in CeAD.—Headache and neck pain are typical clinical features and often the first symptom of CeAD, which emphasizes the need for a rapid and accurate diagnosis, to attempt preventing the occurrence of ischemic manifestations. Headache can be isolated in ~8% of CeAD patients and is more common in vertebral CeAD than in carotid CeAD, and in multiple CeAD.[21,56] The main mechanism of headache in CeAD is thought to be the stimulation of pain sensitive receptors caused by the distension of the artery by the wall hematoma.[56] Headaches in CeAD are often referred to as continuous, intense and throbbing.[56] However, they are highly variable in terms of onset (progressive, acute, or thunderclap) and topography (often ipsilateral hemicrania in carotid CeAD, ispilateral hemicrania, occipital, diffuse, or anterior headache in vertebral CeAD). Of importance, case reports[57–65] and cases series[17,56,66] have shown that CeAD was able to trigger secondary migraine attacks, particularly with aura. Indeed, in addition to a few cases of attacks suggestive of migraine without aura,[23,56,58] numerous cases of migraine attacks with aura or aura without headache have been described at the acute phase of the dissection, both in migraineurs and in individuals without any personal history of migraine.[17,56,57,59–63] Most patients described this attack as unique and unusual.[21,56,61,66]

Potential Mechanisms of Secondary Migraine Attacks in CeAD.—The mechanism by which CeAD triggers a symptomatic aura remains unknown. One hypothesis relies on a reduced brain perfusion that lowers the threshold for developing an aura, as suggested by the evaluation of cerebral hemodynamics in individuals with symptomatic migraine attacks with aura that revealed a reduced cerebral blood flow.[17] Animal studies have shown that hypoperfusion induced by microemboli can trigger spreading depression (SD),[67] an intense wave of neuronal and glial depolarization considered to be the electrophysiological substrate of aura.[68,69] Indeed, intracarotid infusion of particulate material of various size and compositions (cholesterol, polystyrene microspheres, air microbubbles) reliably evoked cortical SD in mice. The mechanism involved transient cerebral hypoperfusion, and the probability of SD induction related to the duration and severity of hypoperfusion, without necessarily definite ischemic injury. Indeed, in more than half of the animals that developed an SD, no ischemic lesion was detected by MRI or by a meticulous examination of serial histological sections throughout the brain.[67] Another hypothesis that should be evaluated is that the injured artery could release substances able to activate an SD.

The evidence that attacks of migraine may reveal CeAD (ie, symptomatic migraine attacks) justifies that the diagnosis of CeAD must be considered in migraineurs with unexplained modification of attack characteristics, particularly if the patient complaints of unusual headache features as regards triggers (exertion, trauma), mode of onset (thunderclap), location (cervical pain) or duration (>72 hours) and/or of unusual aura features. The diagnosis must also be considered in persons without previous migraine history when they complain of recent new-onset headache, or of transient positive or negative focal neurologic symptoms, even if the characteristics suggest a first migraine aura.

Modification of the Clinical Course of Migraine after CeAD: Clinical Evidence and Hypothetical Mechanisms.—The occurrence of CeAD can also modify the clinical course of migraine. Indeed, follow-up studies in patients with CeAD, mostly with ischemic manifestations, have emphasized the large number of migraineurs who experienced improvement or even disappearance of migraine attacks after the occurrence of CeAD, with a frequency between 28 and 92%.[18,19,22,23] The mechanisms of this improvement remain unknown and the absence of control patients with stroke not related to CeAD preclude to state if the improvement relied on the CeAD per se or if it was related to the experience of a stressful life event.[23] Likewise, the study of evolution of migraine in subjects who had pain as the only symptom of CeAD would help in our understanding. Aspirin use may also at least partly be involved in this improvement through its migraine prophylactic effects.[70–72] Finally, more seldom de novo migraine can also occur after CeAD, with a frequency that could reach 15%,[18] although this has not yet been systematically evaluated in large series.

CeAD AND RCVS

Clinical Evidence for an Association of CeAD and RCVS.—An association between RCVS and CeAD was initially suggested by a number of case reports[12,73–82] and subsequently confirmed in a prospective cohort of 20 patients with both conditions, representing 12% of consecutive RCVS patients and 7% of consecutive CeAD patients.[83] In this cohort of 20 patients with both RCVS and CeAD, the clinical presentation of RCVS did not differ from that of isolated RCVS for most characteristics, with severe acute headache in all subjects (recurrent in 75% and unique in 25%) and associated neurological signs in 50% (seizure in 20%, transient focal signs in 20% and/or persistent focal signs in 25%). However, in addition to the usual clinical presentation, associated neck pain was present in 75% of cases. Radiological presentation was also close to that of classical RCVS, with brain lesions in 60% of patients (vs 12 to 81% in isolated RCVS) and with a slightly higher frequency of hemorrhagic presentation: cortical subarachnoid hemorrhage in 55% (vs 30 to 34%) and intracerebral hemorrhage in 15% (vs 12 to 20%); ischemic stroke occurred in 20% of patients (vs 6 to 39%) and/or posterior reversible encephalopathy syndrome in 20% (vs 8 to 38%). In contrast, the clinical presentation differed markedly from that of isolated CeAD. Patients with both RCVS and CeAD have a major female preponderance (90%), a high frequency of isolated headache or neck pain (50%) and a low frequency of symptomatic infarcts (5%) whereas patients with isolated CeAD are equally distributed between both sexes or sometimes show a slight male preponderance, have a low frequency (<10%) of headache and/or neck pain is an isolated symptom[56] and a high frequency (79%) of symptomatic ischemic strokes.[84] Furthermore, in the cohort with both conditions, CeAD more often involved multiple vessels (35%) and predominantly implicated vertebral arteries (83%), which is different from classical CeAD where multiple CeAD occur in 13-16% of patients and the internal carotid artery is the most common dissection site.[85] Among precipitant factors and associated conditions in subjects with both RCVS and CeAD, a personal history of migraine was often reported (60%), even more than in patients with CeAD alone (35%)[15] and postpartum was frequently found (28% of women). While migraine and peri- and post-partum are well known susceptibility factors for isolated RCVS and CeAD, they seem to increase the probability of their association, although small numbers precluded formal statistical comparisons.

Potential Mechanisms Underlying the CeAD–RCVS Association.—Actual data preclude us to state whether CeAD may induce RCVS or whether it is the opposite.

The absence of systematic predefined repeated vessel imaging in this cohort of 20 patients with both conditions and the usual delay in the imaging evidence of vasoconstriction,[12] which is often clearly visible only a few days or even weeks after symptom onset, made it impossible to determine which condition occurred first. One case report evidenced a RCVS with normal cervical arteries

before the occurrence of a carotid CeAD.[81] In this case, one might speculate that intracranial arterial stenosis might have induced an increased upstream pressure in cervical arteries leading to CeAD. However, this cannot be generalized. Indirect arguments in favor of CeAD triggering the RCVS include the fact that RCVS, often unilateral, can occur after cervical artery surgery or stenting.[86–88] The underlying mechanisms could be that cervical vessels might release vasoactive substances that trigger RCVS or that the arterial wall distention due to the mural hematoma activates the sympathetic fibers. Furthermore, one may also speculate the existence of a more generalized underlying arterial vulnerability, which may lead, in a variable chronologic order, to both RCVS and CeAD. One hypothesis could be that arterial vulnerability may induce dysfunction or tearing within the wall of small and medium intracranial arteries responsible for RCVS and its frequent intracranial hemorrhagic complications, and within the wall of cervical arteries thus leading to the mural hematoma characterizing CeAD.[83,89]

Finally, the existence of a shared genetic predisposition for RCVS and CeAD, potentially linked to migraine, should be assessed in large genetic studies. Given the low frequency of RCVS this will require important collaborative efforts. Of interest, MTHFR 677TT has also been associated, in a large meta-analysis that included more than 6000 patients and 11,000 controls, to preeclampsia,[90] a disease that is part of the same spectrum as RCVS. Further studies are needed to evaluate whether MTHFR genotype is involved in the coexistence of RCVS, CeAD and migraine, at least in a subset of patients. Likewise, the potential implication of MMP in RCVS could be assessed.

RCVS AND MIGRAINE

In this section, we discuss whether migraineurs have an increased the risk of RCVS, how RCVS may induce migraine attacks and how being a migraineur may modify the clinical expression of RCVS.

The Risk of RCVS in Migraine Might Be Increased.—Whether migraine increases the risk of RCVS remains unknown. A prior history of migraine has been frequently reported among subjects with RCVS (17-27%).[12,91] Given the high prevalence of migraine in the general population (12-15%), and the female preponderance of migraine and of RCVS, further studies are needed to evaluate whether the frequency of migraine among RCVS patients is significantly higher than in age and gender matched referents from the general population. Importantly, some of the vasoactive drugs used in prophylactic (selective serotonin reuptake inhibitors) or acute (triptans and ergots) migraine treatment may, in some circumstances, facilitate the occurrence of RCVS. Indeed, triptans and ergots may aggravate vasoconstriction when taken to alleviate unusual severe headache mistaken for a migraine attack but may also trigger RCVS.[92,93]

Secondary Migraine Attacks in RCVS: Clinical Evidence and Hypothetical Mechanisms.—In addition, besides the classical severe unusual acute headache, RCVS may trigger symptomatic attacks of migraine with aura or aura without headache.[13] The putative mechanism might rely, as mentioned earlier for symptomatic aura related to CeAD, on the lowering of the aura threshold due to cerebral hypoperfusion, which could be related to vasoconstriction. An alternative mechanism relies on RCVS induced subarachnoid hemorrhage. Indeed, subarachnoid hemorrhage has been reported to induce an aura and a possible associated headache in subjects with amyloid angiopathy or aneurism rupture, whether or not they had a past history of migraine.[94–96] Furthermore, experimental studies in rats showing that products of hemolysis are able to induce SD[97] as well as evidence of SD by electrocorticography in patients with subarachnoid hemorrhage[98] further support the potential role of subarachnoid hemorrhage in the occurrence of aura and migraine attacks in RCVS patients. These two mechanisms are in accordance with clinical practice: in our prospective cohort of patients with RCVS, transient progressive positive visual and/or sensory symptoms were reported in patients with or without subarachnoid hemorrhage, some of them having a history of migraine with aura while other experienced these symptoms for the first time (personal data, unpublished).

Migraine Modifies the Course of RCVS: Clinical Evidence and Hypothetical Mechanisms.—Migraine affects the clinical expression of RCVS. In a large prospective study including 89 subjects with RCVS, in which one third had hemorrhagic manifestations (in order of decreasing frequency subarachnoid hemorrhage, intracerebral hemorrhage and subdural hematoma), being a migraineur independently increased the risk of hemorrhagic complications (OR 2.34, 95% IC 1.06, 5.18).[91] Likewise, as mentioned earlier, although small numbers preclude firm conclusions, the higher frequency of migraine history in the series of patients with both CeAD and RCVS[83] than that in series of subjects with isolated RCVS[10,12] or CeAD,[15] suggests that migraine could increase the risk of joint occurrence of both conditions.

Potential Mechanisms Linking Migraine, RCVS and CeAD.—The pathophysiological link between the three conditions remains unknown. Endothelial dysfunction has been demonstrated in migraineurs[99] and is considered to be one of the mechanisms explaining the increased risk of stroke among migraineurs.[100] A recent way to evidence endothelial dysfunction relies on circulating endothelial progenitor cells, which are involved in the regeneration and maintenance of the endothelium and are considered as a biological surrogate marker of vascular function, endothelial dysfunction being associated with a decrease in their number and function. Circulating endothelial progenitor cells number and function have been demonstrated to be decreased in migraineurs in two different studies[101,102] but also in RCVS patients,[103] suggesting that endothelial dysfunction may be a common thread between the two conditions. Using another surrogate marker, a recent study in migraineurs confirmed these results by showing that the level of endothelial microparticles, which are small membrane vesicles released into the circulation by activated or apoptotic endothelial cells, were higher in migraineurs with aura compared with controls.[104] Interestingly, the level of endothelial microparticles was also increased in eclampsia,[105] a disorder which is part of the spectrum of RCVS, further supporting the evidence of an endothelial disorder in the two conditions. Of interest, a potential link with CeAD should also be assessed as a previous study in CeAD patients has suggested the existence of an impaired vasoreactivity related to endothelial dysfunction in migraineurs with CeAD.[18] Further studies are needed to better understand the role of endothelial dysfunction in the three conditions and in their link.

CONCLUSION

Migraine, RCVS and CeAD share common and complex epidemiological, clinical and genetic features, which might explain their association. The strongest available evidence shows that the risk of CeAD is doubled in patients with migraine, without difference in outcomes between migraineurs and non migraineurs with CeAD. Lower quality evidence shows that migraine increases the risk of intracranial hemorrhage in patients with RCVS and of having an associated CeAD.

Similarly to the complex relations between migraine and stroke, data are lacking to conclude whether the increased risk of CeAD and of complicated RCVS applies to patients affected by migraine as a primary headache disorder, or concerns at least in part, patients who have secondary forms of migraine in the setting of acute or chronic arterial disorders.

Advances in our understanding will require a better categorization of the various migraine subtypes using present and future biological, genetic, and imaging markers.

Although most people with migraine will never have a RCVS or a CeAD, the presently available data also show that these two acute vascular conditions can manifest with isolated headaches that can easily be mistaken for a severe migraine attack, and with focal aura symptoms that are symptomatic auras, secondary to the vascular condition. Advances in neuroimaging have made the diagnosis of RCVS and CeAD easier, but the role of the physician is crucial in identifying among the many people with headaches those who require extensive investigations.

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