Reversible cerebral vasoconstriction syndrome and cervical artery dissection in 20 patients

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ABSTRACT

Objectives: To describe clinical-radiologic characteristics in a prospective series of patients having both confirmed reversible cerebral vasoconstriction syndrome (RCVS) and cervical artery dissection (CeAD).

Methods: From January 2004 to December 2011, from our prospective cohorts of RCVS and CeAD, we studied patients with both conditions.

Results: Of 173 RCVS cases and 285 CeAD cases, 20 patients (18 women, 2 men; mean age 41 years) had both RCVS and CeAD. Main associated conditions were migraine (12/20) and postpartum (5/18). Clinical features included severe headache in all patients, neck pain in 15, focal neurologic deficit in 9, and seizures in 4. Pain was the only symptom in 10 patients. All patients had multifocal cerebral vasoconstriction. There were brain lesions in 12 patients, cortical subarachnoid hemorrhage in 11, posterior reversible encephalopathy syndrome in 4, intracerebral hemorrhage in 3, and infarcts in 4. CeAD involved one artery in 13 patients and multiple arteries in 7. CeAD mostly affected vertebral arteries (25 of 30 CeAD). Only one vertebral CeAD was associated with a related symptomatic infarct. At 3 months, 18 patients had fully recovered, all patients showed reversal of cerebral vasoconstriction, and 21 dissected arteries had normalized, whereas 9 arteries showed residual stenosis (7) and/or aneurysm (3).

Conclusion: The association of RCVS and CeAD was found in 12% of our patients with RCVS and 7% of our patients with CeAD. Underlying mechanisms are unknown. In practice, our results point to the need for a systematic study of both cervical and intracranial arteries in the 2 conditions.
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GLOSSARY

CeAD = cervical artery dissection; **cSAH** = cortical subarachnoid hemorrhage; **ICH** = intracerebral hemorrhage; **PRES** = posterior reversible encephalopathy syndrome; **RCVS** = reversible cerebral vasoconstriction syndrome.

The association of reversible cerebral vasoconstriction syndrome (RCVS) with cervical artery dissection (CeAD) has been reported in a few cases.[1–8] To enhance recognition, we describe clinical-radiologic characteristics of this association in a prospective series of 20 patients.

METHODS

Inclusion criteria. According to ongoing protocols, we recruited patients fulfilling criteria for confirmed RCVS[9] and for CeAD[10] from 2004 to 2011. Confirmed RCVS was defined by severe headaches with or without focal deficits or seizures, multifocal vasoconstriction on cerebral magnetic resonance, CT, or transfemoral angiography with ≥2 narrowings per artery on ≥2 arteries, and normalized angiography within 3 months.[9] Each angiography was assessed by ≥2 coauthors. CeAD was evidenced by mural hematoma on MRI T1 fat saturation and/or string sign, intimal flap, or aneurysm on cervical CT, magnetic resonance, or transfemoral angiography.[10] Clinical data were collected, and migraine was diagnosed as previously described.[9,10] RCVS was "postpartum" when starting within 4 weeks after childbirth.

Standard protocol approvals, registration, and patient consents. All patients signed written informed consent. According to the French national guidelines, this observational study did not require ethics committee approval.

Literature review was performed to identify cases of CeAD and RCVS either confirmed as defined above, or possible, defined by recurrent thunderclap headache and normal brain MRI, or cortical subarachnoid hemorrhage (cSAH) or posterior reversible encephalopathy syndrome (PRES) without evidenced cerebral vasoconstriction.[11]

RESULTS

Of 173 patients (121 women) with confirmed RCVS and 285 patients (142 women) with CeAD, 20 patients (18 women) had both conditions (table 1). Ten patients were recruited from our emergency

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Table 1 Characteristics of 20 patients with confirmed RCVS and CeAD

Case-sex/age, y	Associated conditions	Clinical features (n)[a]	Brain lesions on MRI	Stenosis on intracranial arteries	Dissected cervical arteries	Antithrombotic treatment
1-F/43	None	Neck pain before TCH (2), BP surge	None	RACA, MCAs, PCAs, PICA	RVA	Yes
2-F/26	Postpartum	Neck pain before TCH (2)	cSAH, PRES	Distal ICAs, ACAs, MCAs, PCAs, RVA	RVA	No
3-F/49	Hypercholesterolemia	TCH (4), BP surge	None	ACAs, MCAs, PCAs, PICAs	RVA	No
4-M/38	Cannabis use	TCH (6) before neck pain	None	MCAs, PCAs	RVA	Yes
5-F/36	MO, tobacco use, oral contraceptive	TCH (4) before neck pain, seizure, TIA (4), BP surge	cSAH, PRES	ACAs, MCAs, PCAs	Both ICAs, both VAs	No
6-F/35	MO, postpartum	TCH (1), focal deficit >24 h	cSAH, ICH	ACAs, MCAs, PCAs	RVA	No
7-F/54	MO, paroxetine use, hypercholesterolemia	TCH (1), focal deficit >24 h	cSAH, ICH, infarct	ACAs, MCAs	RVA	No
8-F/45	MO, tobacco use, hypertension, URTI	TCH (5)	cSAH	ACAs, MCAs	Both ICAs	No
9-M/35	Hypertension, tobacco use	TCH (1) and neck pain, focal deficit >24 h	cSAH, infarct	ACAs	LVA	Yes
10-F/43	MO	TCH (5) before neck pain, BP surge	None	PCAs, BA	Both VAs	Yes
11-F/38	MO, postpartum	TCH (2) before neck pain, focal deficit >24 h, seizure	cSAH, PRES	PCAs, PICAs	Both VAs	No
12-F/53	MO, hypercholesterolemia	Neck pain before TCH (5)	None	ACAs, MCAs	RVA	No
13-F/46	MO, neck manipulation, URTI, tobacco/cannabis/ephedrine use	Neck pain before TCH (3), transient visual aura	cSAH	ACAs, 2 MCAs, BA	RVA	No
14-F/46	None	Neck pain before TCH (5), TIA (2), BP surge	cSAH, infarct	ACAs, MCAs	RVA	No
15-F/48	MA, tobacco use	TCH (3) before neck pain, transient sensory aura	None	LACA, LPCA	RVA	Yes
16-F/47	None	TCH (4) before neck pain, BP surge	None	ACAs, PCAs	LVA	Yes
17-F/29	MA, neck manipulation	TCH (4) before neck pain	None	ACAs, MCAs, LPCA, BA	Both VAs	Yes
18-F/40	Postpartum, bromocriptine for 2 d, tobacco use	TCH (1) before neck pain, seizure, BP surge	PRES	ACAs, MCAs	Both VAs	Yes
19-F/47	MO	TCH (1), persistent deficit, seizure	cSAH, ICH, infarct	ACAs, MCAs, PCAs, BA	RICA, both VAs	No
20-F/32	MO, postpartum, cabergoline for 2 d	Neck pain before TCH (3)	cSAH	ACAs, MCAs	LVA	No

Abbreviations: ACA = anterior cerebral artery; BA = basilar artery; BP = blood pressure; CeAD = cervical artery dissection; cSAH = cortical subarachnoid hemorrhage; ICA = internal carotid artery; ICH = intracerebral hemorrhage; LACA = left anterior cerebral artery; LPCA = left posterior cerebral artery; LVA = left vertebral artery; MA = migraine with aura; MCA = middle cerebral artery; MO = migraine without aura; PCA = posterior cerebral artery; PICA = posterior-inferior cerebellar artery; PRES = posterior reversible encephalopathy syndrome; RACA = right anterior cerebral artery; RCVS = reversible cerebral vasoconstriction syndrome; RICA = right internal carotid artery; RVA = right vertebral artery; TCH = thunderclap headache; URTI = upper respiratory tract infection (recent); VA = vertebral artery.
[a] BP surge = BP >160/90 mm Hg.

headache center and 10 from our stroke unit. Cases 1 to 7 were previously partly reported.[4] Mean age was 41 years. Main associated conditions were migraine (60%), tobacco smoking (30%), postpartum (28% of women), and vasoactive substances exposure (15%).

All patients had severe bilateral headaches, with nausea or vomiting in 11 patients. Fifteen subjects had recurrent thunderclap headache, and 5 subjects had a single headache. Fifteen patients had neck pain, which started a mean of 10 days (range 1–31 days) before headache in 5 patients, concomitantly with headache in one patient, and after headache in 9 patients. Head and/or neck pain was the only clinical symptom in 10 patients, whereas the 10 others had associated neurologic signs. Four subjects had seizures. Five subjects had persistent focal deficits, which occurred at headache onset in 4 cases and the next day in one. Four patients had transient focal symptoms lasting <24 hours (TIA or aura-like), which occurred from 10 to19 days after headache onset.

Cerebral vasoconstriction was evidenced by magnetic resonance angiography (19 patients), computed tomography angiography (9 patients), and/or transfemoral angiography (10 patients). Twelve patients had

brain lesions, 11 had cSAH, 4 had PRES, 3 had intracerebral hemorrhage (ICH), and 4 had infarcts. Infarcts were associated with cSAH in all 4 cases, with ICH in 2 cases, and were located in territories of dissected arteries in 3 patients, of whom one had corresponding focal signs.

CeAD was diagnosed before RCVS in 3 patients, at the same time in 10, and after RCVS in 7. CeAD involved one artery in 13 patients and multiple arteries in 7, summing to 30 CeADs affecting 25 vertebral and 5 internal carotid arteries. CeAD was evidenced by mural hematoma in 25 arteries, which angiographies showed occlusion (1), irregularities (4), string sign (6), aneurysm (7), and/or long tapered stenosis (12), or by string sign in 3 arteries (one with long tapered stenosis) or by aneurysm in 2. At least one vertebral CeAD was present in 19 patients, and involved mostly V2 and V3 parts with intracranial extension to V4 in only one patient. Carotid CeAD involved the infrapetrous part of the artery.

Nineteen patients received nimodipine. Antithrombotic treatment, mostly aspirin, was prescribed to 7 of the 9 patients without intracranial hemorrhage, and was not prescribed to 10 of the 11 patients with hemorrhage. One patient with a mild cSAH received aspirin because of a symptomatic infarction in the territory of a dissected artery. Treated patients (8) had no further hemorrhage; untreated patients (12) had no infarct.

At 3 months, any severe pain had resolved; 18 patients had a modified Rankin Scale (mRS) score of 0. Cases 6 and 7 had modified Rankin Scale score of 2 and 3, respectively, from an ICH. Vasoconstriction had resolved in all patients. Twenty-one of 30 dissected arteries had normalized and 9 arteries had not, showing residual stenosis (7) and/or aneurysm (3). Available data from the literature are summarized in table 2.

DISCUSSION The association of RCVS and CeAD was observed in 12% of patients with RCVS and 7% of patients with CeAD consecutively recruited over 8 years in our institution. Because both conditions are individually rare, our findings add to the 9 reported cases,[1–3,5–8] and strongly suggest that the association of RCVS and CeAD is unlikely to occur by chance. Our results might be explained by our dual recruitment (headache center and stroke unit) and by the systematic study of cervical arteries in patients with RCVS and of cerebral arteries in patients with CeAD, with repeat imaging when headache worsens or recurs.

RCVS with CeAD seems to affect middle-aged adults with a female preponderance close to that observed in some RCVS series,[3] but at variance to the usual nearly equal sex distribution of CeAD.[12] Migraine, the most frequent associated condition in our patients, is known to have an increased frequency in both RCVS[11] and CeAD.[2,12] Postpartum, a precipitant in our series and in reported cases, is an established trigger of both RCVS[1,11] and CeAD.[12] Susceptibility factors for both RCVS and CeAD could also increase the risk of their association. By contrast, vasoactive substance use, a precipitant of RCVS but not of CeAD, pertained to only 15% of our patients.

Table 2 Characteristics of reported cases with RCVS and CeAD including 5 cases (1–5) with confirmed RCVS and 4 cases (6–9) with possible RCVS

Case-sex/age, y	Associated conditions	Clinical features	Brain lesions on MRI	Stenosis on intracranial arteries	Dissected cervical arteries	Antithrombotic treatment
1-F/31[1]	Postpartum	Recurrent TCH, seizures, BP surge	PRES	LICA, ACAs, MCAs, PCAs	LICA	md
2-F/md[3]	md	Recurrent TCH	md	Multiple	LVA	md
3-F/44[5]	Neck manipulation, cannabis/tobacco use, recent hypertension	TCH, persistent deficit, BP surge	Infarct	ACAs, MCAs, PCAs	LICA	Yes
4-F/38[7]	Cerebral venous thrombosis, postpartum with bromocriptine	Recurrent TCH, transient deficit, BP surge	Cerebral venous thrombosis	MCAs, PCAs	RICA	Yes
5-F/41[8]	Migraine, postpartum, postdural puncture syndrome, blood-patch	Headache before neck pain	SAH	All intracranial arteries	RICA	Yes
6-F/38[2]	Migraine, postpartum, hypercholesterolemia, urinary tract infection	Bilateral headache, Horner syndrome	cSAH	Not described	RICA	md
7-F/38[2]	Migraine, postpartum, hypercholesterolemia, fever	TCH, TIA, BP surge	cSAH, PRES	Not described	Both VAs	md
8-md/md[6]	md	Recurrent headaches	cSAH	Not described	RVA	md
9-md/md[6]	md	Mild headache, transient deficit	cSAH	Not described	Both ICA	md

Abbreviations: ACA = anterior cerebral artery; BP = blood pressure; CeAD = cervical artery dissection; cSAH = cortical subarachnoid hemorrhage; ICA = internal carotid artery; LICA = left internal carotid artery; LVA = left vertebral artery; MCA = middle cerebral artery; md = missing data; PCA = posterior cerebral artery; PRES = posterior reversible encephalopathy syndrome; RCVS = reversible cerebral vasoconstriction syndrome; RICA = right internal carotid artery; RVA = right vertebral artery; SAH = subarachnoid hemorrhage; TCH = thunderclap headache; VA = vertebral artery.

Clinical presentation and brain MRI features of our patients were that of a typical RCVS, with only a slightly higher frequency of cSAH (50%) than in large series (30%).[11]

By contrast, CeAD was unusual. Multiple CeADs seemed frequent (35%).[12] Vertebral arteries were predominantly affected (83%) contrasting with the usual carotid preponderance of dissections (70%).[13] Clinical presentation was mostly restricted to neck pain, with only one symptomatic infarct, at variance with the usual frequency (67%) of infarcts in vertebral CeAD.[13] This benign pattern of vertebral CeAD probably explains the overall good outcome in our series, much closer to that of RCVS[11] than to that of usual CeAD.[12,13]

There is no evidence-based treatment for RCVS or for CeAD.[11,12] In patients with both conditions, it seems logical to associate nimodipine and antithrombotic drugs, provided there is no intracranial hemorrhage.

We could not elucidate whether RCVS or CeAD started first. One reported case showed evidence of RCVS occurring first.[8] RCVS likely involves a sympathetic deregulation of cerebral arterial tone.[11] RCVS could induce dissection in susceptible persons by increasing pressure upstream of multiple intracranial stenosis, or by altering vessel wall vasa vasorum. Conversely, a dissection might release vasoactive substances triggering RCVS. RCVS is related to PRES,[11] which mainly affects the posterior circulation likely because its autonomic control is lower than that of the carotid circulation. This difference could explain the vertebral artery predilection of dissection in RCVS. Another hypothesis would be that of an arteriopathy, possibly genetically determined, underlying both conditions, although cerebral arteries were found normal in lethal cases of RCVS.[11]

Although our 20-patient series is the largest so far, firm conclusions regarding features of RCVS with CeAD and risk factors will require multicentric larger series and comparisons with control groups including respectively RCVS patients and CeAD patients. Further studies are needed to clarify the mechanisms underlying this association, and to determine optimal treatment strategies.

AUTHOR CONTRIBUTIONS

J. Mawet, M.-G. Bousser, and A. Ducros drafted and revised the manuscript. M.-G. Bousser and A. Ducros designed the study. J. Mawet, M. Boukobza, J. Franc, M. Sarov, M.-G. Bousser, and A. Ducros acquired, analyzed, and interpreted data. M. Arnold acquired, analyzed, and interpreted data and revised the manuscript. A. Ducros supervised the study.

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