Triple and quadruple spontaneous cervical artery dissection: presenting characteristics and long-term outcome

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ABSTRACT

Background: Spontaneous cervicocephalic artery dissection (sCAD) of more than two cervical arteries is rare.

Patients and methods: Vascular and potential sCAD risk factors, triggering events, clinical and neuroimaging findings, and outcome of patients with multiple sCAD were studied. Patients were drawn from prospective hospital-based sCAD registries.

Results: Of 740 consecutive patients with sCAD, 11 (1.5%) had three, and one had four (0.1%) sCAD. Eight of these 12 patients were women. One patient had additional dissections of the celiac trunk and hepatic artery. Vascular risk factors included hypertension (n = 1), hypercholesterolaemia (n = 6), current smoking (n = 5) and migraine (n = 6). No patient had a family history of sCAD, fibromuscular dysplasia (FMD) or connective tissue disease. SCAD was preceded by a minor trauma in five and infection in four patients. Clinical manifestations included ischaemic stroke (n = 8), transient ischaemic attack (n = 3), headache (n = 9), neck pain (n = 4), Horner syndrome (n = 5), pulsatile tinnitus (n = 2) and dysgeusia (n = 1). Brain MRI revealed ischaemic infarcts that affected one vessel territory in seven and two territories in two patients. The 3-month outcome was favourable (modified Rankin scale score 0–1) in 10 patients (83%). No new recurrent stroke or sCAD occurred during a mean follow-up of 50 (SD 29) months.

Conclusion: Multiple sCAD occurred preferentially in women and caused clinical symptoms and signs mainly in one vascular territory. In none of the patients was FMD or any other underlying arteriopathy apparent. The majority of multiple sCAD was preceded by a minor trauma or infection. Clinical outcome was favourable in most patients, and long-term prognosis benign. The data suggest that transient vasculopathy may be a major mechanism for multiple sCAD.

Spontaneous cervicocephalic artery dissection (sCAD) is one of the most frequent causes of stroke in young adults.[1 2] However, the simultaneous occurrence of more than two (multiple) sCAD is rare, with only a few cases with triple or quadruple sCAD.[3–10] Therefore, we aimed to analyse demographic factors, coexisting conditions, potential risk factors, and triggering events, clinical and neuroimaging findings and long-term outcome of our patients with triple or quadruple sCAD.

MATERIAL AND METHODS

Prospectively collected data of consecutive patients presenting with first-ever sCAD at three academic centres, from January 1991 to January 2007 (Zurich and Bern), and from January 1997 to January 2007 (Lariboisière Paris) were analysed. Cervical artery dissections were categorised as spontaneous when occurring spontaneously or associated with an effort or minor trauma.[11 12]

Only patients with at least three sCAD diagnosed within 4 weeks of symptom onset were included in the present study.

The diagnosis of sCAD was established using digital subtraction angiography (DSA) and/or cervical MR imaging with the T1 fat suppression technique and MR angiography (MRA). SCAD was considered proven if the artery showed a string sign (near occlusions of the vessel with decrease or collapse of the lumen distal to a very tight stenosis), an intimal flap or an aneurysm at angiography, and/or a mural haematoma on cervical or cerebral MRI.[13–15] Ischaemic deficits were classified according to their duration as stroke (>24 h) or transient ischaemic attack (TIA; ⩽24 h).

Vascular risk factors, potential risk factors and precipitating events for sCAD were assessed as reported before.[16] In brief, hypertension was defined as a history of antihypertensive treatment or a history of hypertension (systolic blood pressure (BP) >160 mm Hg or diastolic BP >90 mm Hg), or both until September 2000.[16] The new WHO criteria for diagnosis of hypertension (systolic BP >140 mm Hg or diastolic BP >85 mm Hg, or both) were used since October 2000.[17] Hypercholesterolaemia was determined as total cholesterol value >5.2 mmol/l.[16] A family history of stroke or sCAD was defined as a first-degree relative with stroke or sCAD. Migraine with aura or without aura was diagnosed based on the International Headache Society's criteria. Infection was defined as reported previously.[18]

Assessment included a general physical and neurological examination, the National Institute of Health Stroke Scale (NIHSS), routine blood examinations, an electrocardiogram and an examination of the cervicocerebral arteries by angiography and/or MRI/MRA as mentioned above. Location of sCAD was defined by the most proximal arterial segment involved on DSA, MRA and/or cervical MRI.[19] In all patients a cranial MRI was performed. Renal artery imaging was performed at the discretion of the treating physician in nine patients (CT angiography (n = 3); CT angiography and renal DSA (n = 1); CT angiography and MRA (n = 1); MRA (n = 2), renal ultrasound (n = 2)). One patient underwent skin

Table 1 Baseline characteristics, potential risk factors, triggering events, concomitant conditions and clinical findings of 12 patients with triple or quadruple cervical artery dissections

Patient	Age (years)	Sex	Vascular risk factor	Concomitant diseases	Potential triggering events	Dissected vessels (segment)
1	51	M	Current smoking		Gastrointestinal infection and vomiting 12 days prior to sCAD; river rafting 13 days prior to first symptom	VA left (V2)
			Hypercholesterolaemia			VA right (V3)
						ICA right
2	44	F	Current smoking		Respiratory infection 3 days prior to first symptom	VA right (V1, V2)
			Hypercholesterolaemia			ICA left
			Migraine without aura			ICA right
			Family history of stroke			
3	48	F	Past smoking		Forced neck extension during biking 22 days prior to first symptom	VA left (V3)
			Migraine without aura			VA right (V2, V3)
						ICA left
4	46	M	Current smoking	Renal infarction left without evidence of renal artery dissection		VA left (V2, V3)
			Hypercholesterolaemia			ICA left
			Hypertension			ICA right
5	50	F	Hypercholesterolaemia			VA right (V1, V2, V3)
						ICA left
						ICA right
6	27	F	Current smoking		Chiropractic neck manipulation on day of first symptom	VA left (V2, V3)
			Migraine without aura			VA right (V2)
						ICA right
7	41	M	Past smoking		Respiratory infection 14 days prior to first symptom	VA left (V2)
			Hypercholesterolaemia			VA right (V2)
			Migraine without aura			ICA left
8	41	M	Current smoking		Gastrointestinal infection, 5 days prior to first symptom	VA left (V2)
			Hypercholesterolaemia			VA right (V2)
						ICA left
						ICA right
						Hepatic artery
						Celiac trunk
9	50	F	None			VA left (V2)
						VA right (V2)
						ICA left
10	47	F	Migraine without aura			VA left (V2)
						VA right (V1)
						ICA left
11	47	F	None	Morbus Basedow	Fall without head or neck trauma 15 days prior to first symptom	VA right (V2)
						ICA left
						ICA right
12	24	F	Migraine with aura	Essential thrombocythemia	Forced neck extension 21 days prior to first symptom	VA left (V2)
						VA right (V2)
						ICA left

ICA, internal carotid artery; VA, vertebral artery.

biopsy. Antithrombotic treatment included intravenous heparin followed by oral vitamin K antagonists with a target international normalised ratio (INR) of 2.5 (range 2–3) for 6 months in 10 patients. Two patients with large infarcts on MRI were treated with aspirin 100 mg/day for the first 2 weeks. One of the two patients was left on long-term aspirin treatment, and in the remaining patient aspirin was replaced by oral vitamin K antagonists for 6 months. After 6 months, all patients received long-term aspirin (100–300 mg/day) treatment.

Clinical follow-up information 3 months after symptom onset was obtained through neurological examination including the modified Rankin scale score (mRS).[20] Long-term follow-up information was assessed by a structured phone interview by different neurologists and trained neurology fellows. MRS score, recurrent sCAD, stroke and TIA were recorded.

Follow-up extracranial and transcranial ultrasound of the cervical and cerebral arteries was performed in all patients after 3 and 6 months. Recanalisation of the dissected artery was assessed as previously reported.[21 22]

Table 2 Clinical symptoms and signs of 12 patients with triple or quadruple cervical artery dissections

Patient	First symptom and signs	Time to diagnosis	Local symptoms and signs (days before diagnosis)	Ischaemic symptoms and signs (days before diagnosis)
1	Bilateral headache	4 days	Bilateral headache (4)	Posterior circulation TIA with vertigo and vertical diplopia (3)
			Horner syndrome right (0)	Strokes in the territories of both PICA (0)
2	Bilateral headache	7 days	Bilateral headache (7)	Anterior circulation TIA with small DWI lesion in the left MCA territory (0)
3	Neck pain right	22 days	Neck pain right (22)	None
			Bilateral headache (21)	
			Neck pain left (20)	
			Tinnitus left (3)	
4	Bilateral headache	8 h	Bilateral headache (0)	Stroke in the right MCA territory (0)
				Asymptomatic renal infarction on CT scan
5	Neck pain right, and Wallenberg syndrome right	5 days	Neck pain right (5)	Right lateromedullary ischaemic stroke (5)
6	Neck pain right	22 days	Neck pain right (22)	Stroke in the right PCA territory (2)
			Bilateral thunderclap headache (2)	
7	Bilateral neck pain	11 days	Bilateral neck pain (11)	None
			Dysgeusia right (9)	
			Headache right (5)	
			Horner syndrome right (2)	
8	Headache left and Horner syndrome left	4 h	Headache left (0)	Stroke in the right MCA territory (0)
			Horner syndrome left (0)	
9	Headache left, Horner syndrome left	11 days	Headache left (11)	None
			Horner syndrome left (11)	
10	Aphasia and hemiplegia right	6 h	None	Stroke in the left MCA territory (0)
11	Bilateral headache	15 days	Bilateral headache (15)	Stroke in the left MCA territory (0)
			Horner syndrome left (4)	
12	TIA (vertigo)	14 days	Tinnitus left (4)	Posterior circulation TIA (14)
				Stroke in the left MCA territory (4)
				Stroke in the left PICA territory (3)

Time to diagnosis indicates the time to diagnosis of the first spontaneous cervicocephalic artery dissection.
MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar arteries; TIA, transient ischemic attack.

RESULTS

Of a total of 740 sCAD patients, 12 with at least three sCAD (mean age 43 (5) years; range 24–52 years; eight women) were identified: 11 (1.5%) with triple and one (0.1%) with quadruple sCAD. Of these patients, seven had bilateral spontaneous vertebral artery dissection (sVAD) and unilateral spontaneous internal carotid artery dissection (sICAD), whereas four patients had bilateral sICAD and unilateral sVAD. The patient with four sCAD had additional dissections of the hepatic artery and celiac trunk.

The mean interval from symptom onset to diagnosis was 9 days (SD 8 days; range 4 h to 22 days).

Vascular risk factors, concomitant diseases and triggering events are summarised in table 1. Vascular risk factors included hypertension in 1, current smoking in 5, past smoking in 1, hypercholesterolaemia in 6 and a family history of stroke in 1. Six patients had migraine, five without and one with aura. No patient had FMD, family history of connective tissue disease or sCAD. One patient had essential thrombocythemia. SCAD was preceded by a minor trauma in five and an infection (two respiratory and two gastrointestinal) in four patients (table 1).

Clinical manifestations and time course are summarised in table 2. Ischaemic symptoms occurred in nine patients (TIA in 1, TIA followed by ischaemic stroke in 2, and ischaemic stroke in six patients). Brain MRI revealed infarcts in a single vessel territory in seven patients and in two different vessel territories in two patients. No subarachnoid haemorrhage was detected. One patient with a triple dissection (patient 9) had only a painful Horner syndrome. No retinal ischaemia was observed. Local symptoms and signs included headache in nine patients (bilateral in six and unilateral in three), neck pain in four (bilateral in two and unilateral in two), unilateral Horner syndrome in five, unilateral pulsatile tinnitus in two and unilateral dysgeusia in one. One patient with ischaemic stroke suffered a renal infarction without demonstration of renal artery dissection.

In the 10 patients who underwent cervical MRI, 30 of 31 dissections were diagnosed by a mural haematoma, and one VAD was diagnosed by a typical string sign on DSA. In the two other patients, who did not undergo cervical MRI, triple sCAD was diagnosed by DSA. All 17 sICAD were typically located distally to the carotid bulb in the cervical segment The most frequent location of sVAD was the V2 segment (n = 15), followed by the V1 segment (n = 3) and the V3 segment (n = 2). No intracranial sVAD or sICAD was observed. DSA or MRA showed occlusion of nine (24%) dissected arteries, stenosis of 25 (67%) and the association of aneurysm and stenosis of three (9%).

The outcome after 3 months was favourable (mRS 0 or 1) in 10 patients (83%). Two patients remained disabled, one with mRS 2 and one with mRS 4. No patient suffered a recurrent stroke or a recurrent CAD after a mean-follow-up of 50 months, SD 29 months (median 50, range 14–98 months).

Follow-up ultrasound after 6 months revealed complete recanalisation of 29 (78%) dissected vessels, residual stenosis in six (16%) and persistent occlusion of two (5%) dissected vessels. Of the nine initially occluded arteries, three showed complete recanalisation, four showed partial recanalisation, and

two remained occluded. Of the 28 initially stenosed arteries, 26 recanalised completely and two partially. Aneurysm persisted in all three patients, and no new aneurysm was observed.

DISCUSSION

In this study, dissection of more than two cervical arteries was a rare event (1.6% of all sCAD). This is in line with previous case series.[4]

Two-thirds of the patients with three or four sCAD were women. This finding is in agreement with the results of a previous study reporting 11 of 13 patients with both vertebral and carotid artery dissection to be women.[4] Furthermore, we recently reported that women with sCAD were more likely to have two or more sCAD than men.[23]

The occurrence of multiple sCAD suggests the presence of an underlying intrinsic arteriopathy. However, in the present study, no patient with multiple sCAD had FMD, hereditary connective tissue disease or a family history of sCAD. The overall high frequency of migraine (50%) was similar to that reported in previous case-control studies.[24 25] Potential precipitating events such as infection and/or minor trauma were present in two-thirds of our patients. Such an association of triple or quadruple sCAD with a preceding trauma or infection has been described in single cases.[5 26] During a mean follow-up of 50 months, no recurrent stroke or recurrent sCAD occurred. The association of simultaneous multiple dissections with potential precipitating events in two-thirds of the patients without evidence of underlying vasculopathy and without recurrent events over 4 years suggests a transient vasculopathy as the prevailing pathogenetic factor in triple or quadruple sCAD. However, we cannot exclude the coexistence of a predisposing arteriopathy, such as FMD or connective tissue disorders, because not all patients underwent DSA, renal artery imaging and skin biopsy, and even in patients with DSA, the diagnosis of underlying FMD may be overlooked.[27] Furthermore, our study is limited by its small sample size and the long inclusion period. Moreover, our study provides no reliable epidemiological data because this is not a population-based study. Nevertheless it is likely that patients with triple or quadruple sCAD are referred to a tertiary care centre.

The majority of patients presented with ischaemic stroke in a single vessel territory, and only two patients had ischaemic strokes in the territory of two dissected arteries. No new ischaemic symptoms occurred after diagnosis of sCAD and initiation of antithrombotic treatment, and the clinical outcome was favourable in most patients. Moreover, follow-up ultrasound showed complete reacanalisation in 78% of the dissected vessels. These findings suggest that antithrombotic treatment is sufficient in most cases with multiple sCAD, although ultrasound may not detect residual non-haemodynamically relevant stenosis. Endovascular treatment may be an option in cases with insufficient collaterals and progressive or new ischaemic symptoms despite antithrombotic treatment.[7]

In conclusion, two-thirds of patients with triple or quadruple sCAD were women. The majority of multiple sCAD were preceded by a minor trauma or an infection and caused ischaemic stroke in a single vessel territory. In none of the patients was an underlying arteriopathy apparent. Clinical outcome was mostly favourable without any recurrent stroke or sCAD. No recurrence was observed during a 4-year follow-up. Our data suggest that transient vasculopathy may be a major mechanism in multiple sCAD.

Competing interests: None.

Ethics approval: Ethics approval was provided by Cantonal Ethics Committees Bern and Zurich, Switzerland; Local Ethics Committee, Lariboisière Saint-Louis, Paris.

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