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Primary headaches and painful spontaneous cervical artery dissection

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Abstract The relation between primary headaches (PH) and pain related to spontaneous cervical artery dissection (SCAD) is still unclear, as well as the progress of PH after dissection.
To investigate this relation, the characteristics of pain related to SCAD and changes in PH patterns after SCAD, we evaluated 54 consecutive patients. Thirty-five (65%) had previous PH. Painful SCAD occurred in 39 (72%). Frontal and parietal localizations were significantly associated with internal carotid artery dissection (p=0.013 and p=0.010, respectively), whereas occipital and nuchal pain, with vertebral artery dissection (p=0.047 and p<0.001, respectively). Previous PH did not influence the presence of pain at SCAD onset. Twenty-six (74%) patients with PH reported improvement in PH pattern after a mean follow-up of 32 months. These results suggest that mechanisms underlying PH do not modulate dissection-related pain. Disruption of perivascular afferents may be involved in improvement of PH patterns after SCAD.

Keywords Artery dissection • Carotid • Vertebral artery • Primary headaches • Migraine • Stroke

Introduction

The role of migraine as a potential risk factor for spontaneous cervical artery dissection (SCAD) was emphasized by three case-control studies [1–3]. Headache, facial or neck pain are common presenting symptoms of SCAD, although mechanisms underlying dissection-related pain remains incompletely understood [4–8]. The relationship between previous migraine and painful SCAD was investigated in only two studies with opposite findings and therefore it is still a matter of controversy [4, 5].

The progress of primary headaches (PH) after the episode of SCAD has been rarely investigated. Improvement in migraine and tension-type headache (TTH) after SCAD have been reported [5, 9, 10], however the possible interference of the use of prophylactic drugs has not been assessed.

In a series of 54 patients with SCAD, we evaluated the previous history of primary headaches (PH), the presence and the characteristics of pain related to SCAD, the relation between PH and painful dissection, as well as changes in PH pattern after SCAD.

Subjects and Methods

We evaluated patients consecutively admitted to the Neurology Clinical Division of our hospital between 1997 and 2006. Inclusion criteria were: extracranial SCAD diagnosed by magnetic resonance imaging (MRI), magnetic resonance angiography, computed tomography angiography (CTA) or conventional angiography. Extracranial SCAD was based on classical angiographic signs such a irregular stenosis ("string sign"), double lumen or intimal flap, presence of mural hematoma on cervical MRI or CTA within the C1 segment of the internal carotid artery (ICA) or within the V1 to V3 segments of the vertebral artery (VA) [2, 6]. Dissections were considered as spontaneous when they occurred spontaneously or in association with non-traumatic precipitating activity or minor trauma [1]. Isolated intracranial or traumatic dissections (severe blunt head or neck traumas or motor vehicle accidents) were excluded.

Sixty-four patients fulfilled the inclusion criteria and were invited to participate in the study. Ten patients were excluded: four patients who died with ICA dissection (ICAD) (three bilateral ICAD), and six living patients who did not attend clinical interviews (three with unilateral ICAD, two with unilateral VA dissection (VAD) and one with bilateral VAD). Therefore, 54 patients were included (33 men; mean age and SD: 38.6±10.6 years; range, 13 to 57 years). There were 32 patients with ICAD and 22 with VAD (eight with bilateral VAD). In 52 (96%) patients, dissections were associated with ischemic events (IE): 50 with infarcts and two with transient ischemic attacks. During the acute stage of SCAD, 43 patients were treated with anticoagulants, and 11 with antiplatelet drugs. Patients were interviewed with a semi-structured questionnaire. Two patients had mild language impairment and their relatives helped them during the interviews. The patterns of the headaches experienced before, at the time of, and at least 90 days after SCAD were systematically evaluated. Headache characteristics at dissection onset were evaluated in 19 patients at admission, and in the remaining 35, during follow-up. We compared age, gender, frequency of painful dissection, "pain-to-stroke time" and history of PH between patients evaluated during admission (n=19) and those evaluated during follow-up (n=35). No significant difference was found between these patients in any of these variables ($p>0.05$). Data from all patients were grouped for analyses.

Headache, neck or facial pains that preceded the onset of neurological deficits in the ischemic event (stroke or transient ischemic attack) by more than 20 minutes were considered to be related to SCAD. This time was set arbitrarily, according to *Silbert et al.* [5], to exclude stroke-related pain. We calculated the "pain-to-stroke time" as the time between the onset of pain that started and remained continuous or was present daily, and the onset of the IE. The localization, the characteristics of dissection-related headache and the presence of symptoms that could mimick a migraine attack were recorded. Pain intensity in the SCAD episode was quantified by a numerical rating scale (NRS), graded in unit increments from zero (no pain) to 10 (worst pain) [6].

PH was classified according to the International Headache Society criteria [11] by two independent neurologists (C.R.C; M.C.) who interviewed patients separately in different occasions. The final diagnosis was obtained by consensus. Migraine without aura, migraine with aura, and probable migraine were grouped together as "migraine". None of the patients presented chronic migraine. Episodic and probable tension-type headaches were grouped as "TTH". The frequency of any previous PH, migraine or TTH was compared between patients with painful and non-painful dissection.

Pain characteristics before SCAD and after a minimum of 90 days from the IE were evaluated in patients with PH history. The time of 90 days was arbitrarily set in order to prevent a possible interference of stroke-related and dissection-related headache [11]. Patients with a history of PH were asked to compare frequency and intensity of PH pain after SCAD to before the SCAD. Answers were categorized as "worse", "better" or "equal". "Worse" was defined as an increase either in the baseline frequency or in the average intensity (graded in unit increments from zero (no pain) to 10 (worst pain)) of PH episodes reported by the patient during the follow-up interview. "Better" was considered if patient reported either a decrease in the baseline frequency or in the average intensity of PH episodes. "Equal" was considered if no change either in frequency or in the intensity of PH episodes was noticed.

Use of aspirin or prophylactic drugs for PH was investigated in all patients. Prophylactic drugs (beta-blockers, antiepileptic drugs, tricyclic antidepressants, selective serotonin or norepinephrine reuptake inhibitors) were considered present if these drugs had been used on a daily basis for longer than 2 months after dissection. This criterion was arbitrarily defined based on the observation that the efficacy of prophylactic drugs is often noticed at four weeks and may continue to increase for three months, in controlled clinical trials [12]. None of the patients used prophylactic drugs before SCAD. The use of prophylactic drugs or aspirin was compared between patients who had PH improvement and those who did not.

Continuous variables were analyzed by either paired t tests or Mann-Whitney tests according to data distribution, and categorical variables by Chi-square or Fisher exact tests. A p-value < 0.05 was considered significant. The study was approved by the local ethics committee and patients provided written informed consent.

Results

Thirty-five (65%) patients had some type of PH; 14 (40%) had migraine only (four of them had both migraine with

aura and migraine without aura), 13 (37%) had TTH only and 8 (23%) had both types before SCAD.

Painful SCAD occurred in 39/54 (72%) patients. Pain preceded the ischemic event in a median time of 120 hours (5 days; range: 30 minutes to 60 days). Median "pain-to-stroke" intervals were 4 days in ICAD (range, 30 minutes to 60 days), and 6 days in VAD (range, 30 minutes to 28 days). Pain was unilateral in 26 patients (14 unilateral ICAD; 9 unilateral VAD and 3 bilateral VAD). In patients with unilateral dissection, the side of the pain was the same as that of the dissected artery. In 13 patients, pain was bilateral (8, unilateral ICAD; 5, bilateral VAD). Frontal or parietal pain was significantly associated with ICAD (p=0.013 and p=0.010, respectively). Occipital or nuchal pain was associated with VAD (p=0.047 and p<0.001, respectively) (Table 1). Thirty (77%) patients rated the dissection-related pain as severe (NRS ?7/10). Pain was described as pulsating (60%), constrictive (26%), dull (7%), stabbing (5%) and burning (2%). In 13 patients with pulsating headache, pain was associated with nausea or vomiting (7 ICAD; 6 VAD). In three of them (1 ICAD; 2 VAD), there was also photophobia and phonophobia mimicking a migraine attack. Two of these patients (1 ICAD; 1 VAD) had previous history of migraine and reported more severe pain intensity at SCAD onset compared to previous migraine attacks.

There were no significant differences in the frequency of previous history of PH, migraine or TTH between patients with painful and non-painful SCAD. In addition, no significant differences were found in demographical data and clinical features between these groups (Table 2).

After a mean follow-up of 32 months (median: 23.5 months; range 3 to 107 months), 26/35 (74%) patients with previous PH experienced some improvement in frequency or intensity of pain. Ten of these patients had migraine only, ten had TTH only and six had both types of PH prior to SCAD. Thirteen (50%) patients who reported PH improvement had not used prophylactic drugs and/or aspirin. The frequency of use of prophylactic drugs and/or aspirin was not significantly different between patients who experienced improvement PH improvement and those who did not (p>1.0) (Table 3).

Discussion

Most of our patients had intense pulsating or constrictive headache or neck pain as warning symptoms preceding SCAD by a median of five days. This agrees with previous studies [4–8]. In ICAD patients, pain was significantly more frequent in the anterior part of the head, compared to VAD, where pain occurred in the nuchal and/or occipital

Table 1 Localizations and the characteristics of dissection-related pain according to the dissected artery

Pain localization	Artery with dissection		p
	ICA (%) (n=22)	VA (%) (n=17)	
Frontal	14 (64)	4 (23.5)	0.013
Periorbital	1 (4.5)	0	NS
Teeth / Cheek / Ear	4 (18)	0	NS
Parietal	10 (45)	1 (6)	0.010
Temporal	8 (36)	2 (12)	NS
Occipital	6 (27)	10 (59)	0.047
Nuchal pain	2 (9)	12 (70.5)	<0.001
Anterior neck / Throat / Shoulder	2 (9)	1 (6)	NS

ICA: internal carotid artery; *VA*: vertebral artery; *NS*: not significant

Table 2 Demographical data and clinical characteristics of patients with painful and non-painful SCAD. Percentages are in parentheses. p values for all comparisions were >0.05

	Painful (%) (n=39)	Non-painful (%) (n=15)
Age – years (mean)	39.6	36.1
Men	21 (54)	12 (80)
ICAD	22 (56)	10 (67)
Presence of IE	37 (95)	15 (100)
Previous PH (any)	27 (69)	8 (53)
Previous Migraine only	10 (25)	4 (27)
Previous TTH only	11 (28)	2 (13)
Previous migraine and TTH	6 (15)	2 (13)

Table 3 Progress of PH in 35 patients with SCAD and previous PH, according to the type of PH and the daily use of prophylactics or aspirin. Percentages are shown in parentheses. Comparisions between patients with and without improvement showed p-values >0.999

	Progress of PH	
	With improvement (n=26)	Without improvement (n=9)
Previous type of PH		
Migraine only	10 (38.5)	4 (44)
TTH only	10 (38.5)	3 (33)
Both types	6 (23)	2 (23)
Prophylactics or aspirin		
Yes	13 (50)	4 (44)
No	13 (50)	5 (56)

region. The anterior location of the pain in ICAD may be explained by stretch, distortion and ischemia of the pericarotid plexus and the posterior location of the pain in VAD may be due to lesion of upper cervical nerves involved to the perivascular innervations of the arteries of the posterior fossa [5]. Both routes converge into the trigeminovascular system, implied in the referral of vascular pain (visceral inputs) to superficial tissues (somatic forehead inputs). This system is also a final common pain pathway to migraine, cluster, and other headache syndromes [13, 14]. Our results suggest that preactivation of this system by PH does not influence whether or not a patient will have pain at SCAD presentation.

Three patients with painful dissection had pulsating headache associated with nausea or vomiting, photophobia and phonophobia. These could mimick an attack of migraine without aura. Two of these patients had previous migraine. In the third patient, the unusually severe pain could have raised the suspicion of secondary headache. However the diagnosis of SCAD was made only after the IE.

It has been argued that migraine may predispose patients to development of headaches at stroke onset [13, 15]. The exact mechanism is unknown. In 65 patients with ICAD, it was observed that previous history of migraine was more frequent in patients with painful dissection than in patients with non-painful dissection [4]. In this study, SCAD-related pain was defined as any pain that occurred before, during or after the IE. The same definition was used by Silbert et al, but no association was found by the authors between migraine and painful dissection in patients with ICAD or VAD [5]. In contrast with both studies, we defined dissection-related pain as headache or cervical pain that started *before* the IE. In this manner, we aimed to avoid classifying pain related to the stroke itself as a dissection-related pain. Similarly to Silbert et al [5], we did not find a significant relation between previous migraine or TTH and painful dissection.

PH improvement after SCAD occurred in most patients and was not influenced by use of prophylactic drugs. Improvement in PH pattern after cerebrovascular diseases was described in a small series of patients who had migraine with aura and who presented migrainous cerebral infarction [16]. The same was also observed in a patient with an anterior communicating artery aneurysm who had an extensive surgical dissection of pericarotid sympathetic fibers of the supraclinoid carotid [17]. It is plausible that the change in PH pattern may be caused by dissection-related disruption of a perivascular pathway involved in referral of visceral and somatic inputs in PH [10].

This study has some limitations. First, the retrospective evaluation of PH may be associated with recall bias. However, considering that patients are more likely to remember experiences that were moderately to extremely bothersome during the acute phase of their disease [18] we believe that it is likely that their recall ability might be accurate, as most of our patients experienced a stressful situation: the stroke. Second, in the absence of data from a group of patients with stroke of other etiologies, one can not determine whether PH improvement was specific to SCAD or whether it was related to the experience of a stressful life event. Third, the comparison between frequency and intensity of PH *before* and *after* SCAD did not include any quantitative data, only subjective judgement of patients about the progress of their PH.

In conclusion, headache or neck pain was frequent in SCAD and the localization varied according to the dissected vessel. SCAD pain mimicked a migraine attack in three patients. The history of migraine or any type of PH did not influence pain characteristics at dissection onset. This suggests that mechanisms underlying PH do not modulate dissection-related pain. Further data gathered in multicentric studies with a greater number of patients are necessary in order to confirm these findings. Such studies are necessary to provide further information about mechanisms underlying PH, SCAD and their relation.

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