Clinical import of Horner syndrome in internal carotid and vertebral artery dissection

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ABSTRACT

Objective: To study the prognostic importance of Horner syndrome (HS) in patients with internal carotid artery dissection (ICAD) or vertebral artery dissection (VAD).

Methods: In this observational study, characteristics and outcome of patients with ICAD or VAD from the CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) database were analyzed. The presence of HS was systematically assessed using a standardized questionnaire. Patients with HS (HS+) were compared with HS− patients. Crude odds ratios (ORs) with 95% confidence intervals and ORs adjusted for age, sex, center, arterial occlusion, bilateral dissection, stroke severity, and type of antithrombotic treatment were calculated.

Results: We analyzed 765 patients (n = 496 with ICAD, n = 269 with VAD, n = 303 prospective, n = 462 retrospective). HS was present in 191 (38.5%) of the patients with ICAD and 36 (13.4%) of the patients with VAD ($p < 0.001$). HS+ ICAD patients presented less often with stroke or TIA ($p < 0.001$), less often had bilateral ($p = 0.019$) or occlusive ($p = 0.001$) dissections, and had fewer severe strokes ($p = 0.041$) than HS− ICAD patients. HS+ ICAD patients had a better functional 3-month outcome than those without HS ($OR_{crude} = 4.0$ [2.4–6.7]), and also after adjustment for outcome-relevant covariates ($OR_{adjusted} = 2.0$ [1.1–4.0]). HS+ ICAD patients were less likely to have new strokes than HS− ICAD patients ($p = 0.039$). HS+ VAD patients more often had vessel occlusion ($p = 0.014$) than HS− patients but did not differ in any of the other aforementioned variables.

Conclusion: In patients with ICAD, HS is an easily assessable marker that might indicate a more benign clinical course. HS had no prognostic meaning in patients with VAD. ***Neurology*®** **2014;82:1653–1659**

GLOSSARY

CADISP = Cervical Artery Dissection and Ischemic Stroke Patients; **CeAD** = cervical artery dissection; **CI** = confidence interval; **HS** = Horner syndrome; **ICAD** = internal carotid artery dissection; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **VAD** = vertebral artery dissection.

Cervical artery dissection (CeAD) is defined by the presence of a hematoma within the wall of the internal carotid or vertebral artery.[1] The enlarged vessel wall may cause narrowing of the lumen, prompting stenosis or occlusion. Eccentric expansion of the bulged arterial wall may entail a variety of nonischemic symptoms,[2–5] including Horner syndrome (HS). In patients with internal carotid artery dissection (ICAD), HS is thought to result from compression of the pericarotid sympathetic plexus.[6] Although the pathophysiology is different, HS has also been reported in some patients with vertebral artery dissection (VAD),[7–9] presumably as a sign of

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brainstem stroke.[10] However, no large-scale studies on the presence of HS in VAD are available.[11]

Prior studies have demonstrated that patients with ICAD without ischemic events are more likely to present with HS than those with stroke or TIA.[6,12] This observed inverse association between HS and cerebral ischemic events can be explained in different ways. First, the association might be true, with the implication that HS flags a milder subtype of ICAD, possibly due to the location of the hematoma more in the outer layers of the arterial wall. Second, the inverse association might be artificial and explained by recognition biases: in patients with severe stroke, HS may be overlooked—which seems plausible, in particular in patients with incomplete HS[13]—whereas CeAD in patients with neither stroke nor HS might remain unrecognized.[14]

In patients with VAD (without an accompanying ICAD), the presence of HS indicates an ischemic lesion of central sympathetic fibers, most frequently via a brainstem stroke. The differences in the pathogenesis of HS in ICAD and VAD might be helpful to understand and explain the prognostic meaning of HS in patients with CeAD.

With these considerations in mind, we analyzed clinical characteristics and outcome among patients with ICAD with and without HS from the multicenter CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) database. Findings were compared with the data of patients with VAD with and without HS from the same database.

METHODS The CADISP Study Group recruited consecutive patients evaluated in neurology departments with a diagnosis of CeAD or non-CeAD-stroke patients, as well as healthy subjects, across 18 centers in 8 countries (Argentina, Belgium, France, Finland, Germany, Italy, Switzerland, and Turkey).[15] Patients were recruited both prospectively and retrospectively.[16,17] All patients (those recruited retrospectively and those recruited prospectively) received the same diagnostic approach and follow-up evaluations. Prospectively recruited patients were asked to participate as soon as they could give informed consent, which was an ethical requirement. Functional outcome was assessed by outpatient visits or telephone calls using the modified Rankin Scale (mRS) at 3 months.[18] Patients recruited retrospectively had their CeAD before the enrolling center joined the CADISP clinical study.[16] Their clinical data, including 3-month outcome data, had been ascertained systematically in local databases or registries.[17]

For the current study, all patients with CeAD were eligible, if (1) presence or absence of HS was recorded, and if information about (2) 3-month outcome, (3) stroke severity, and (4) use or nonuse of anticoagulation (i.e., vitamin K antagonists, IV heparin, or low-molecular-weight heparin) as first antithrombotic treatment[18] was available. First antithrombotic treatment was defined as first treatment after the diagnosis of stroke or of CeAD (in patients presenting with solely local symptoms). Patients with combined ICAD plus VAD were excluded.

The following standardized variables were used from the CADISP database[15,16] as done in prior research: age, sex, center, site of dissection (i.e., ICAD vs VAD), bilateral vs unilateral dissection, family history of young stroke (defined as any stroke in first-degree relatives younger than 50 years), type of presenting symptom, which included stroke, TIA, HS (defined as presence of pupillary miosis and blepharoptosis with or without facial anhidrosis[19]), headache, and neck pain, stroke severity among those presenting with stroke as assessed by the NIH Stroke Scale (NIHSS) score (for patients with CeAD without stroke, NIHSS score = 0 was used), presence or absence of vessel occlusion,[6,12] the use of anticoagulation as first antithrombotic treatment in the acute phase,[20] occurrence of new stroke during the 3-month follow-up period, and functional 3-month outcome using the mRS. Age and stroke severity at admission (NIHSS) were used as continuous variables in the analyses. A favorable 3-month outcome was defined as an mRS score of 0 or 1.

Statistical analyses. The aforementioned variables were compared between HS+ and HS− patients with ICAD and patients with VAD, respectively, using Student *t*, Mann-Whitney *U*, and χ^2 tests as appropriate. Crude odds ratios (ORs) with 95% confidence intervals (CIs) for favorable 3-month outcome were calculated for HS+ compared with HS− patients. In addition, ORs were adjusted for age, sex, center, and—taking into account the potential prognostic importance of these variables—vessel occlusion,[6,7] bilateral occurrence of CeAD, NIHSS score,[18] and anticoagulation as first antithrombotic treatment[20–22] using multivariable logistic regression models. SPSS version 19 (IBM Corp., Armonk, NY) was used for all statistical analyses.

Standard protocol approvals, registrations, and patient consents. The CADISP study protocol (http://clinicaltrials.gov/ct2/show/NCT00657969) was approved by competent local authorities of all participating centers and is conducted according to the national rules concerning ethics committee approval and informed consent.

RESULTS The CADISP database comprised 983 patients with CeAD. We excluded 187 patients from the study because of missing information about presence or absence of HS (n = 28), stroke severity at admission (n = 128), functional outcome after 3 months (n = 43), and initial anticoagulation as first antithrombotic treatment (n = 33). Forty-five patients were excluded because 2 or more of the above-mentioned variables were missing. From the remaining 796 patients, we excluded 31 further patients for having combined ICAD plus VAD. The final study sample comprised 496 patients with ICAD (64.8%) and 269 patients with VAD (35.2%) (table 1). Enrollment was prospective in 198 ICAD and 105 VAD patients, and retrospective in 298 ICAD and 164 VAD patients.

HS was present in 191 (38.5%) of the patients with ICAD and 36 (13.4%) of the patients with VAD ($p < 0.001$); HS+ ICAD patients were more

Table 1 Baseline characteristics among patients with ICAD and VAD stratified to presence or absence of HS

	ICAD without HS (n = 305)	ICAD with HS (n = 191)	p	OR[a] (95% CI)	VAD without HS (n = 233)	VAD with HS (n = 36)	p	OR[a] (95% CI)
Sex, female	136 (44.6)	64 (33.5)	0.015		110 (47.2)	19 (52.8)	0.593	
Age, y	45.2 ± 10.3	47.0 ± 8.5	0.040		40.9 ± 10.1	43.6 ± 10.5	0.137	
Stroke or TIA	260 (85.2)	70 (36.6)	<0.001	0.09 (0.06-0.15)	208 (89.3)	36 (100.0)	0.032	Not determined
NIHSS score[b]	4 (0-25)[c]	2 (0-22)[c]	0.041	0.95 (0.91-1.00)	1 (0-24)[c]	2 (0-6)[c]	0.347	0.95 (0.86-1.06)
Cervical pain	111 (36.5)	89 (46.6)	0.013	1.67 (1.11-2.49)	157 (67.4)	22 (61.1)	0.607	0.81 (0.35-1.84)
Headache	194 (63.6)	144 (75.4)	0.003	1.92 (1.24-2.98)	151 (64.8)	22 (61.1)	0.829	1.09 (0.49-2.44)
Occlusive CeAD	117 (38.4)	43 (22.5)	0.001	0.46 (0.29-0.72)	70 (30.0)	18 (52.8)	0.014	2.88 (1.24-6.69)
Bilateral CeAD	37 (12.1)	12 (6.3)	0.019	0.41 (0.20-0.87)	34 (14.6)	5 (13.9)	0.828	1.13 (0.37-3.44)
Pseudoaneurysm	38 (12.5)	34 (17.8)	0.123	1.55 (0.89-2.70)	19 (8.2)	4 (11.1)	0.705	1.28 (0.36-4.50)
Anticoagulation[d]	242 (79.3)	145 (75.9)	0.375	0.94 (0.55-1.59)	198 (85.0)	30 (83.3)	0.804	1.68 (0.48-5.89)
Diagnostic delay[b]	3 (0-67)	4 (0-107)	0.019	1.03 (1.00-1.05)	2 (0-65)	1 (0-31)	0.595	0.98 (0.92-1.05)
FH young stroke	15 (5.1)	4 (2.3)	0.056	0.28 (0.08-1.04)	2 (0.9)	2 (5.7)	0.108	7.92 (0.63-98.9)

Abbreviations: CeAD = cervical artery dissection; CI = confidence interval; FH = family history; HS = Horner syndrome; ICAD = internal carotid artery dissection; NIHSS = NIH Stroke Scale; OR = odds ratio; VAD = vertebral artery dissection.

Data are n (%), mean ± SD, or median (range). Diagnostic delay = median number of days (range) between onset of symptoms and hospitalization. FH young stroke = FH ischemic stroke at younger than 50 years in first-degree relatives.

[a] ORs and 95% CIs were adjusted for age, sex, and center of inclusion.

[b] Stroke severity at admission (NIHSS score) and diagnostic delay were summarized with median values (range).

[c] Stroke severity was calculated after exclusion of nonischemic patients.

[d] Anticoagulation as first antithrombotic treatment.

often men, presented less often with stroke or TIA ($p < 0.001$), and presented more often with cervical pain and headache than HS− ICAD patients. HS+ patients less often had bilateral ICADs ($p = 0.019$), less often had ICAD occlusion ($p < 0.001$), had fewer severe strokes ($p = 0.041$), and showed a trend to a lower frequency of a family history of young stroke ($p = 0.056$) than HS− ICAD patients.

Contrary to the observations in patients with ICAD, HS+ VAD patients more often had vessel occlusion ($p = 0.014$) than HS− VAD patients. No other variables were different between HS+ and HS− patients with VAD (table 1).

Fourteen study patients—10 with ICAD and 4 with VAD—had new strokes during the 3-month follow-up period. New strokes were less likely in ICAD HS+ patients compared with HS− patients ($p = 0.039$); however, no such difference was observed in patients with VAD (table 2).

No deaths occurred during the 3-month follow-up period. Functional outcome was favorable in 585 patients (76.5%) from the study sample. The distribution of mRS scores in patients with ICAD and VAD stratified for absence or presence of HS is shown in the figure.

HS+ patients with ICAD were more likely to have a favorable functional 3-month outcome than HS− patients ($p < 0.001$; OR_{crude} [95% CI] = 4.0 [2.4–6.7]; table 2). This difference remained significant after adjustment for age, sex, center, vessel occlusion, bilateral CeAD, initial NIHSS score, and anticoagulation as first antithrombotic treatment ($p = 0.024$; $OR_{adjusted}$ [95% CI] = 2.0 [1.1–4.0]). HS+ and HS− patients with VAD did not differ regarding 3-month outcome with and without adjustments (table 2).

DISCUSSION This observational study of HS in patients with ICAD and VAD yielded the following 4 key findings. First, HS was present in more than one-third of the patients with ICAD and in one-seventh of the patients with VAD. Second, patients with ICAD and HS presented less often with stroke or TIA and had fewer severe strokes (in case of stroke) than HS− ICAD patients, while no such differences were found between HS+ and HS− VAD patients. Third, in patients with VAD, vessel occlusion was more common in those presenting with HS. In contrast, vessel occlusion was less common in patients with ICAD and HS. Fourth, HS was an independent outcome predictor and a possible indicator of a low stroke risk in patients with ICAD but not in patients with VAD.

Our observation that more than every third patient with ICAD had HS confirmed the results from prior series (8/32 = 25%,[9] 29/78 = 37%,[23] 234/533 = 44%[24]). HS was reported in some small series of patients with VAD with differing frequencies

Table 2 Outcome at 3 months in patients with ICAD and VAD with and without HS

Outcome variables	ICAD without HS (n = 305)	ICAD with HS (n = 191)	p	OR (95% CI)	VAD without HS (n = 233)	VAD with HS (n = 36)	p	OR (95% CI)
New stroke	9 (3.0)	1 (0.5)	0.097	0.17 (0.02–1.38)	3 (1.3)	1 (2.8)	0.502	2.19 (0.22–21.7)
Adjusted for age, sex, and center			0.070	0.14 (0.02–1.18)			0.724	1.61 (0.12–22.3)
Multiple adjustments[a]			0.039	0.10 (0.01–0.89)			0.580	2.52 (0.10–66.4)
Favorable outcome[b]	199 (65.5)	168 (88.9)	<0.001	4.03 (2.44–6.67)	187 (80.3)	31 (83.8)	0.664	1.23 (0.48–3.13)
Adjusted for age, sex, and center			<0.001	4.21 (2.47–7.19)			0.317	1.68 (0.61–4.62)
Multiple adjustments[a]			0.024	2.01 (1.10–3.99)			0.284	1.80 (0.61–5.30)

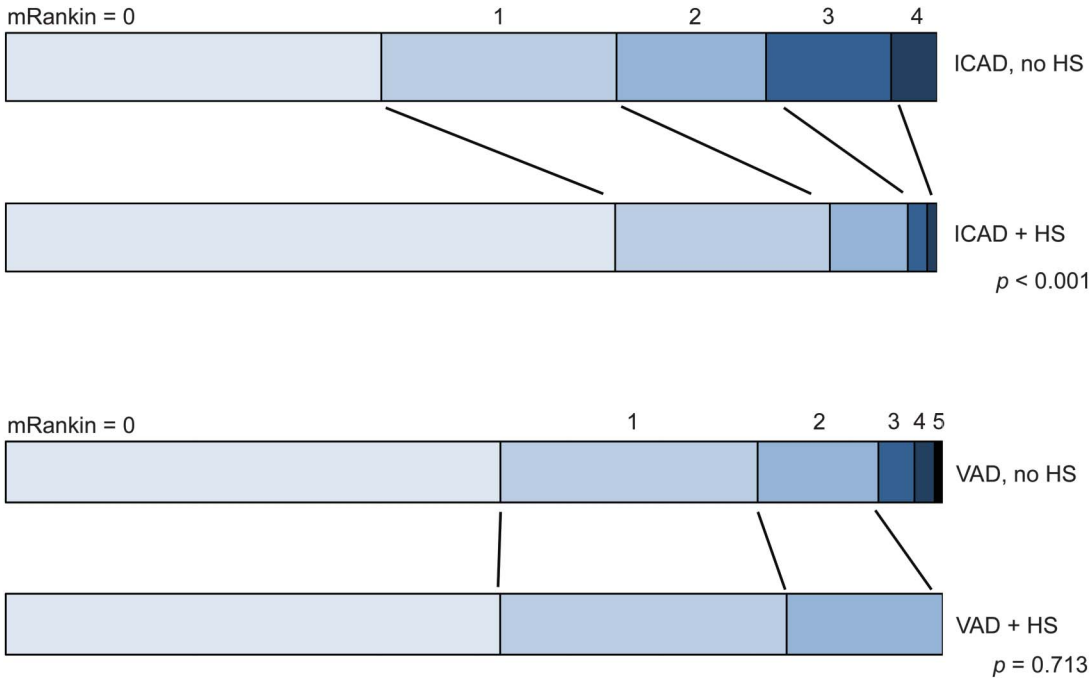
Abbreviations: CI = confidence interval; HS = Horner syndrome; ICAD = internal carotid artery dissection; OR = odds ratio; VAD = vertebral artery dissection.
Data are n (%) unless otherwise indicated.
[a] Multiple adjustments include adjustment for age, sex, center, stroke severity (initial NIHSS score), vessel occlusion, bilateral cervical artery dissection, and anticoagulation (as first antithrombotic treatment).
[b] Favorable outcome refers to modified Rankin Scale score of 0 or 1 at 3 months.

(0/46 = 0%,[23] 1/13 = 8%,[7] 1/4 = 25%,[8] 4/18 = 22%[9]) while the presence or absence of HS was not reported in 2 larger-scale VAD series.[25,26] This study shows that HS is not a rarity but a relevant clinical sign. In this context, our findings may be used as an argument to increase the awareness to make the diagnosis of HS at the bedside, in particular in young adults presenting with neck discomfort, warranting further diagnostic vascular imaging.

The observation that HS+ ICAD patients presented less often with stroke than HS− patients confirms the findings of earlier studies.[6,7] More importantly, our study adds that HS was associated with lower stroke severity in case of ischemia. In addition, HS was a predictor of favorable 3-month outcome, independent of other outcome-relevant variables including stroke severity, age, and vessel occlusion. Moreover, HS+ ICAD patients had fewer new strokes within 3 months than HS− patients. None of these associations was observed in patients with VAD.

The observed differences in predictive importance of HS in ICAD vs VAD patients may be explained by

Figure Distribution of 3-month modified Rankin scale scores in patients with ICAD and VAD stratified for presence or absence of HS



HS = Horner syndrome; ICAD = internal carotid artery dissection; mRankin = modified Rankin scale score at 3 months; VAD = vertebral artery dissection.

differences in the pathogenesis of HS between the 2 sites of dissection. In ICAD, HS is thought to result from impairment of the pericarotid sympathetic plexus.[6,19] Thus, in patients with ICAD and HS, the mural hematoma might preferentially affect outer layers of the arterial wall, which might be less likely to cause ischemic events than hematomas in the inner layers. Nevertheless, aneurysmal ICAD was not more common in HS+ than in HS− patients with ICAD. In patients with VAD, on the contrary, the presence of HS indicates a central sympathetic lesion revealing an ischemia usually of the brainstem, or, less frequently, of the spinal cord or of (hypo) thalamic structures.[26]

Given the equipoise in the general neurology community about the optimal antithrombotic treatment in patients with CeAD, our findings suggest that the presence of HS might indicate a more benign clinical course in ICAD. It will be important to investigate within randomized controlled trials, e.g., CADISS,[21] whether the presence of HS or other clinical predictors of disease outcome modify the effect of antithrombotic treatment.

We are aware of the following further limitations. First, HS may be underreported in VAD where it is usually associated with other severe signs of brainstem infarction and could be overlooked. Because HS+ patients were reported from nearly all centers, it is unlikely that this limitation jeopardized our key findings. Second, we did not record any details about HS, including whether HS was complete, and if not, which parts of the triad were present. Furthermore, it is unknown whether HS resolved or not during follow-up. Thus, we are not able to analyze whether ICAD and VAD differed in these HS characteristics, and whether they might have any prognostic importance. Third, the absence of any deaths at 3 months indicates that we studied a selected CeAD population. Severely affected patients were less likely to participate because giving informed consent was an ethical requirement for participation in this study. Fourth, as a consequence, we were limited in evaluating the prognostic meaning of HS in the subgroup of patients with ICAD with severe strokes. While the entire group of HS+ ICAD patients had a point estimate of the OR for favorable 3-month outcome of 4.0, that of the subgroup of HS+ ICAD patients with NIHSS score >10 was 5.7. Even though the latter was not clinically significant ($p = 0.08$), it points to the same direction and is suggestive of a favorable outcome. Finally, detailed neuroimaging data about intracranial arteries were not available. Thus, we could not clarify whether HS in patients with VAD was associated with occlusion of the posterior inferior cerebellar artery.

This observational study showed that HS is a frequent sign in patients with CeAD. Its prognostic import differed with the location of the dissection. In patients with ICAD, HS may suggest a lower risk of stroke within the next 3 months and higher odds for a favorable 3-month outcome. In patients with VAD, HS was not associated with outcome or with ischemic complications.

AUTHOR CONTRIBUTIONS

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Dr. Tatlisumak is immediate past editor-in-chief of *Case Reports in Neurology*, serves on the editorial boards of *Stroke*, *Cerebrovascular Diseases*, *Current Vascular Pharmacology*, *The Open Pharmacology Journal*, *Clinics of Turkey*, *Clinics of Turkey/Neurology*, *The Open Cardiovascular Medicine Journal*, *Recent Patents on Biotechnology*, *Recent Patents on CND Drug Discovery*, *Experimental and Translational Stroke Medicine*, *Stroke Research and Treatment*, *BMC Journal of Experimental and Translational Stroke Medicine*, and *Frontiers in Stroke*. Dr. Tatlisumak has filed patents re: stanniocalcin proteins and nucleic acids and methods based thereon, new therapeutic uses (method to prevent brain edema and reperfusion injury), and thrombolytic compositions (method to prevent postthrombolytic hemorrhage formation). 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