ORIGINAL ARTICLE

Prognostic significance of pulsatile tinnitus in cervical artery dissection

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Background and purpose: Our aim was to investigate whether pulsatile tinnitus (PT) in cervical artery dissection (CeAD) has prognostic significance.
Methods: All CeAD patients from the CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) study with documentation of PT were analysed. The presence of PT was systematically assessed using a standardized questionnaire. Stroke severity at admission was defined according to the National Institutes of Health Stroke Scale (NIHSS). Excellent outcome after 3 months was defined as a modified Rankin Scale of 0–1.
Results: Sixty-three of 778 patients (8.1%) reported PT. PT+ patients presented less often with ischaemic stroke (41.3% vs. 63.9%, $P < 0.001$), more often with dissection in the internal carotid artery (85.7% vs. 64.2%, $P = 0.001$), less often with vessel occlusion (19.0% vs. 34.1%, $P = 0.017$) and more often with excellent outcome at 3 months (92.1% vs. 75.4%, $P = 0.002$). Logistic regression analysis identified PT as an independent predictor of excellent outcome after 3 months [odds ratio (OR) 3.96, 95% confidence interval (CI) 1.22–12.87] adjusted to significant outcome predictors NIHSS on admission (OR 0.82, 95% CI 0.79–0.86), Horner syndrome (OR 1.95, 95% CI 1.16–3.29) and vessel occlusion (OR 0.62, 95% CI 0.40–0.94) and to non-significant predictors age, sex, pain and location of CeAD.
Conclusion: The presence of PT in CeAD is associated with a benign clinical course and predicts a favourable outcome.

Introduction

Cervical artery dissection (CeAD) is a major cause of stroke in young and middle-aged patients, responsible for up to 25% of ischaemic strokes. Besides stroke, CeAD presents with local signs that might occur solely or in addition to stroke symptoms. Local signs

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include headache, neck pain, Horner syndrome, cranial nerve palsy, cervical-root injury and pulsatile tinnitus (PT)[1–3]. PT has been observed in about 5%–15% of CeAD patients, perhaps favouring female sex [4–6]. Dissections in the carotid system are about three times more often associated with PT than dissections in the vertebral artery system [4]. Different causes can lead to blood flow accelerations and local turbulence that may result in the perception of PT. The most probable reason for PT upon CeAD is higher grade stenosis of the affected artery [7,8]. Here, patients from the CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) study were analysed to investigate whether PT has prognostic significance in CeAD patients.

Methods

The CADISP consortium enrolled 983 CeAD patients in 18 neurological centres in eight countries, both prospectively and retrospectively (for more details see [9,10]). At study entry, detailed signs and symptoms of each participant were recorded using a standardized questionnaire [10]. This questionnaire included the variable 'presence or absence of PT', which was used for the current study. PT was defined as the experience of perceiving sounds without any known audible external sound, coinciding with the patient's heartbeat lasting for more than 5 min [11,12]. Stroke severity on admission was assessed with the National Institutes of Health Stroke Scale (NIHSS). For patients without ischaemia a dummy value of NIHSS = 0 on admission was set, as well as for patients without stroke but with transient ischaemic attack with missing NIHSS value. Outcome at 3 months was defined as excellent if modified Rankin Scale (mRS) was 0–1. Vessel occlusion was detected via contrast enhanced magnetic resonance angiography, computed tomography angiography or ultrasound or using a combination of them. The parameter pain included both neck pain and headache. In the current study patients with reported presence or absence of PT and with documentation of stroke severity on admission and functional outcome at 3 months were included. One patient with dissection of the common carotid artery was excluded.

Statistical analysis

PT+ patients were compared with PT− patients. Normally distributed data are presented as mean and standard deviation (SD), non-normally distributed data as median and range. For categorical variables, counts and percentages are given. Data were compared with Student's t test, the Mann−Whitney U test or the Fisher exact test where appropriate. Logistic regression analysis was used to analyse the association between PT and outcome after adjustment for age, sex, NIHSS, Horner syndrome, pain, location of the dissection and vessel occlusion. Because NIHSS and stroke both reflect ischaemic infarction and both are significantly different according to PT, only NIHSS was used for further analysis due to additional information of stroke severity. Crude odds ratios (ORs) with 95% confidence intervals (95% CIs) and ORs adjusted for potential confounders were calculated. A two-sided P value <0.05 was considered statistically significant. Statistical analysis was performed with the Statistical Package for the Social Sciences, SPSS (SPSS Inc., 23.0 for Windows, IBM, Armonk, NY, USA).

Ethics

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

Results

In all, 778 CeAD patients with documented information about PT, NIHSS and mRS at 3 months comprised the final study sample. 63 patients (8.1%) reported PT (PT+ patients), 29 of 311 (9.3%) prospectively enrolled patients and 34 of 467 (7.3%) retrospectively enrolled patients ($P = 0.348$). PT+ patients were more likely to be female (65.1% vs. 41.6%, $P < 0.001$) and were less likely to present with ischaemic stroke (41.3% vs. 63.9%, $P = 0.001$). Amongst the PT+ patients, 54 (77.8%) had dissections in the internal carotid artery, compared to 459 (60.6%) of the PT− patients ($P = 0.001$). Moreover, five patients (7.9%) in the PT+ group and 26 patients (3.6%) in the PT− group had dissections in both internal carotid artery and vertebral artery. Thus the total proportions of internal carotid artery dissection were 85.7% and 64.2% ($P = 0.001$), respectively. Occlusion was less frequent in PT+ patients than in PT− patients (19.0% vs. 34.1%, $P = 0.017$). Median mRS after 3 months was 0 in PT+ patients versus 1 in PT− patients ($P = 0.016$). Excellent outcome after 3 months favoured PT (92.1% vs. 75.4%, $P = 0.002$). The rate of recurrent stroke was low and not different between the PT− and PT+ groups [15 (2.1%) vs. 0, $P = 0.627$] (Table 1).

Logistic regression analysis identified PT as a predictor for excellent outcome after 3 months (OR 3.96,

Table 1 Patients' characteristics and outcome according to pulsatile tinnitus (PT)

	No PT (n = 715)	PT (n = 63)	P
Age, mean (SD)	44.2 (10.2)	44.8 (9.3)	0.66[a]
Female sex	296 (41.6%)	41 (65.1%)	<0.001[b]
Stroke	457 (63.9%)	26 (41.3%)	0.001[b]
TIA	164 (22.9%)	17 (27.0%)	0.441[b]
NIHSS on admission, median (range)	2 (0–25)	1 (0–18)	0.275[c]
Purely local symptoms (no ischaemia)	148 (20.7%)	27 (42.9%)	<0.001[b]
Pain (neck pain/headache)	579 (81.0%)	53 (84.1%)	0.616[b]
Horner syndrome	206 (28.8%)	24 (38.1%)	0.149[b]
ICAD	433 (60.6%)	49 (77.8%)	0.001[b]
VAD	256 (35.8%)	9 (14.3%)	
ICAD+VAD	26 (3.6%)	5 (7.9%)	
Occlusion	244 (34.1%)	12 (19.0%)	0.017[b]
PT as the only symptom	n.a.	3 (4.8)	
mRS 3 months, median (range)	1 (0–5)	0 (0–3)	0.016[c]
Excellent outcome (mRS 0–1)	539 (75.4%)	58 (92.1%)	0.002[b]
Recurrent stroke	15 (2.1%)	0	0.627

ICAD, internal carotid artery dissection; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack; VAD, vertebral artery dissection. The analysis of NIHSS on admission was restricted to the subgroup of patients with ischaemia. [a]Student's t test; [b]Fisher's exact test; [c]Mann–Whitney U test.

Table 2 Logistic regression analysis with excellent outcome (mRS 0–1) as dependent variable

	OR	95% CI	P
Age	0.98	0.96–1.00	0.065
Male sex	1.45	0.94–2.24	0.115
NIHSS on admission	0.82	0.79–0.86	<0.001
Pulsatile tinnitus	3.96	1.22–12.87	0.026
Horner syndrome	1.95	1.16–3.29	0.012
Pain (neck pain/headache)	0.91	0.53–1.55	0.722
Occlusion	0.62	0.40–0.94	0.025
Location (ICA vs. VA)[a]	1.03	0.65–1.62	0.957

CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR odds ratio. Location site of dissection: ICA, internal carotid artery; VA, vertebral artery. [a]Patients with CeAD in both ICAD and VAD are not included in the regression analysis.

95% CI 1.22–12.87). The association between PT and outcome was independent from other significant outcome predictors such as NIHSS on admission (OR 0.82, 95% CI 0.79–0.86), Horner syndrome (OR 1.95, 95% CI 1.16–3.29) and vessel occlusion (OR 0.62, 95% CI 0.40–0.94) and from non-significant predictors such as age (OR 0.98, 95% CI 0.96–1.00), male sex (OR 1.45, 95% CI 0.94–2.24), pain (OR 0.91, 95% CI 0.53–1.55) and location of CeAD (Table 2).

Discussion

In this study PT was associated with a favourable outcome in patients with CeAD. PT+ patients had an almost four-fold increased likelihood of an excellent outcome compared to those without PT. Presence of PT was also associated with female sex, lower likelihood of stroke, fewer arterial occlusions and fewer dissections in the vertebral artery. Logistic regression analysis showed PT to be an independent predictor for excellent outcome adjusted for age, sex, NIHSS, Horner syndrome, pain, vessel occlusion and location of CeAD.

In this study the focus was on easily assessable clinical parameters (age, sex, NIHSS, Horner syndrome, pain and PT) to allow the treating physician to gain a quick overview of patients' characteristics which might be associated with more benign course. As recently reported for Horner syndrome, PT is associated with a more benign clinical course of CeAD [13]. Our study did not attempt to discover the mechanism behind PT in CeAD but rather described the authentic clinical situation in these patients.

Although PT is less frequently reported than other local signs such as pain or Horner syndrome, it was not rare, being reported by 8.1% of our patients. Because PT predicts favourable outcome, it should be of interest and physicians should specifically ask for its presence. The underlying cause of a newly occurred PT is in up to 20% cervical artery stenosis or aneurysm [8,14]. Thus a newly occurred PT should lead clinical and vascular examination to exclude underlying CeAD. PT was the only clinical sign of CeAD in three of our patients. In addition, a newly occurred PT in the course of CeAD might indicate changes in vessel status like revascularization of an occlusion or vice versa. In our analysis PT predicted favourable outcome independent of vessel occlusion. This might be surprising because PT is supposed to be related to vessel status, especially to high grade stenosis. One

could therefore speculate that PT might be a surrogate of non-occlusion of the affected vessel and this fact drives the association of PT and favourable outcome. But this could not be excluded or confirmed by our data. It is not known in how many tinnitus patients the vessel status (occlusion/stenosis of various degrees) was the same (i) at the time of vascular imaging and (ii) at the time of occurrence of tinnitus; the time course of PT was not recorded. Thus for example late occurrence or disappearance in the course of PT could not be analysed. This is the main limitation of our study. The prognostic significance of PT is not yet understood and the interpretation remains speculative.

Another major limitation of our study is the lack of information about the degree and the detailed location (i.e. arterial segment) of the stenosis. Comparing retrospectively and prospectively included CeAD patients PT reporting was within the same range of 7%–9%. This might indicate that selection bias in reporting PT is not crucial. However, under-reporting of PT in severely affected patients cannot be excluded.

Conclusion

The presence of PT in CeAD is associated with a benign clinical course with lower probability of stroke, less severe strokes and better outcome at 3 months.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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Appendix

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