Hacking stroke in women: towards aetiology-driven precision prevention

Os, H.J.A. van

11. Role of atherosclerosis, clot extent, and penumbra volume in headache during ischemic stroke

Hendrikus J. A. van Os, Irene C. van der Schaaf, L. Jaap Kappelle, Brigitte K. Velthuis, Alexander Broersen, J. A. Vos, Gisela M. Terwindt, Michel D. Ferrari, Ale Algra, Marianne A. A. van Walderveen, Marieke J. H. Wermer

Neurology. 2016 Sep 13;87(11)

Abstract

Background and purpose: To investigate the role of large vessel atherosclerosis, blood clot extent, and penumbra volume in relation to headache in ischemic stroke patients

Methods: In this cross-sectional study, we performed non-contrast CT, CT-angiography (CTA), and CT-perfusion (CTP) in 284 participants from the Dutch acute stroke study and Leiden Stroke Cohort within 9 hours after ischemic stroke onset. We collected headache characteristics prospectively using a semi-structured questionnaire. Atherosclerosis was assessed by evaluating presence of plaques in extra- and intracranial vessels and by quantifying intracranial carotid artery calcifications. Clot extent was estimated by the clot burden score on CTA and penumbra volume by CTP. We calculated risk ratios with adjustments (aRR) for possible confounders using multivariable Poisson regression.

Results: Headache during stroke was reported in 109/284 (38%) participants. Participants with atherosclerosis in the extracranial anterior circulation less often had headache than those without (35% versus 47%; RR:0.72;95%CI:0.54–0.97). Atherosclerosis in the extracranial posterior circulation and in the intracranial arteries was also associated with less headache, but these associations were not statistically significant. Penumbra volume (aRR:1.08; 95%CI:0.63-1.85) and clot extent (aRR:1.02; 95%CI:0.86-1.20) were not related with headache.

Conclusions: Headache in the early phase of ischemic stroke tends to occur less often in patients with atherosclerosis than in patients without atherosclerosis in the large cerebral arteries. This finding lends support to the hypothesis that vessel wall elasticity is a necessary contributing factor in the occurrence of headache during acute ischemic stroke.

Introduction

Acute ischemic stroke is frequently associated with concomitant headache but the underlying mechanisms are largely unknown.[1-5] Several hypotheses have been put forward, including a crucial role for blood vessel wall elasticity because ischemic stroke-associated headache is less common in older patients and in patients with hypertension.[1, 3, 5-7] Direct pressure on the vessel wall, e.g. by a large blood clot, is another possible mechanism as headache is a common feature during balloon inflation and wire manipulation in neurointerventional procedures.[8, 9] Several studies have shown that headache during acute ischemic stroke is more common in patients with ischemia in the posterior circulation or with a history of migraine, which possibly might be attributed to increased susceptibility to spreading depolarizations (SDs).[5, 7] SDs are slowly spreading waves of intense neuroglial depolarizations associated with profound changes in cerebral blood flow.[10] They are the likely underlying mechanism for migraine aura and a putative trigger for migraine headache by stimulating sensory afferents of the trigeminovascular system.[11, 12] SDs may also occur in the penumbra of large middle cerebral artery infarctions[13] and may thus potentially activate headache-generating mechanisms.[4, 13, 14]

In the present study we performed non-contrast CT (NCCT), CT-angiography (CTA) and CT-perfusion (CTP) to assess the association of atherosclerosis of large cerebral arteries, clot extent and penumbra volume with headache concomitant to acute ischemic stroke in a large cohort of well characterized stroke patients.[15] We tested the following three hypotheses: (i) if stiffness of cerebral arteries would protect against headache, then ischemic stroke-associated headache would be expected to be less common in patients with atherosclerosis than in patients without; (ii) if vasodilatation of large vessels is important, then patients with high clot extent are expected to more frequently have headache associated with ischemic stroke than patients with low clot extent; and (iii) if SDs are involved, patients with large cortical penumbras are expected to experience more often headache than patients with small penumbra volumes.

Methods

Patients

We included patients from the Dutch acute stroke study (DUST), a large prospective multicenter cohort study performed between May 2009 and August 2013.[15-18] The aim of DUST was to investigate the value of CT-angiography (CTA) and CT-perfusion (CTP) for predicting outcome after ischemic stroke. Inclusion criteria for the study were: age ≥18 years, onset of stroke symptoms <9 hours and NIHSS ≥2 or

≥1 if intravenous thrombolysis with rtPA was indicated. Exclusion criteria were known renal failure and contrast agent allergy.[15] For the current study, patients from 5 of the 14 participating DUST centers (Leiden University Medical Center (LUMC), University Medical Center Utrecht, Medical Center Haaglanden, VU University Medical Center and the St. Antonius Hospital Nieuwegein) were asked to answer questions from a headache questionnaire upon admission. The inclusion period was from May 2012 until August 2013. In the LUMC, patients from the Leiden Stroke Cohort who underwent non-contrast CT (NCCT), CTP and CTA according to the DUST protocol but who could not be included in DUST because they already participated in another study were also approached for participation in the headache study. In LUMC, inclusion for the headache study also continued after conclusion of DUST from August 2013 until March 2014. All patients were prospectively included with the same imaging protocol and questionnaires. All patients underwent NCCT, CTA and CTP on admission with standardized scan protocols between centers. Scan parameters of the NCCT were: 120 kVp, 300 mAs and 1 mm reconstructed slice thickness. For CTA 60–80 ml of contrast agent (300 mg I/ml) was injected into the antecubital vein (18-gauge needle) at a rate of 6 mL/s followed by a 40-mL saline flush at a rate of 6 mL/s. The scan parameters for the CTA were: 120 kVp, 150 mAs and 1 mm reconstructed slice thickness. Radiologic parameters were assessed by trained neuroradiologists with good inter observer variability.[15]

Standard protocol approvals, registrations, and patient consents

DUST was approved by the Medical Ethical Committee of the participating hospitals. In addition, the Medical Ethical Committee of LUMC approved the headache research protocol. Informed consent was obtained from all patents for use of the data.

Patient characteristics

We assessed the following clinical baseline characteristics during admission: demographic features, cardiovascular risk factors, a history of cardiovascular disease or migraine, baseline National Institutes of Health Stroke Scale (NIHSS) and blood pressure on admission. NIHSS ≥7 was used to distinct between mild and moderate/ severe stroke. Stroke-to-imaging time was recorded and measured in minutes. Clinical outcome was prospectively assessed by telephone with the modified Rankin Score (mRS) at 3-month follow up. Good outcome was defined as mRS ≤ 2.

Headache questionnaire

Headache characteristics were collected during admission by research nurses with a semi-structured questionnaire. The questionnaire contained the following questions:1. Did you have headache during or shortly after the ischemic stroke? 2. At what time exactly did the headache appear? 3. Did you have this type of headache before? 4. What kind of headache did you experience during the ischemic stroke? 5. What was the location of the headache? 6. How long did the headache last? 7. Were there any concomitant symptoms? Patients who answered 'I don't remember' at question 1 were excluded from the study. The time between hospital admission and filling in of the questionnaire was registered.

Radiological parameters

We identified patients with any sign of atherosclerosis in extracranial and intracranial vessel segments of the anterior and posterior circulation on CTA. Extracranial vessel segments were divided into anterior (common and internal carotid arteries) and posterior circulation (vertebral arteries). Signs of atherosclerosis were defined as non-calcified, calcified or mixed plaque. We measured intracranial atherosclerotic burden by assessing intracranial internal carotid artery (ICA) calcification volume, using calcium as a measure for atherosclerosis since these two parameters are highly correlated.[19] Intracranial ICA calcification was quantified by measuring calcium volumes from the petrous part to the top of the intracranial carotid arteries on NCCT using dedicated software (customized research version of CalcScore V11.1 by Medis Specials bv, The Netherlands). After setting a threshold, regions of interest were drawn to discern intracranial ICA calcifications from the skull base. A small pilot study was performed to find an optimal threshold for visually discerning ICA calcifications from the skull base on NCCT. Since DUST was a multicenter study with CT data from different vendors, we tested several thresholds on 10 randomly selected data sets per center. We found the optimal threshold to be 160 Hounsfield units, which resulted in a spread of ICA calcification volume data that did not notably vary between centers. Continuous intracranial ICA calcification volume data were subsequently divided into tertiles (small, medium and large ICA calcification volume). The presence of a clot was assessed in both the anterior and posterior circulation. In addition, for the anterior circulation the clot burden score (CBS) was assessed on CTA. The CBS is a scoring system to evaluate the extent of thrombus in the anterior circulation by location and scored on a scale 0-10. A score of 10 is normal, implying clot absence; a score of 0 implies complete multi-segment vessel occlusion. Two points should be subtracted if thrombus is found in the supraclinoid ICA, proximal and distal M1 segment. One point should be subtracted if thrombus is found in the infraclinoid ICA, ACA or for each of the M2 branches.[20] For the

patients with an anterior circulation stroke confirmed on CTA the CBS was subdivided into tertiles of clot extent. Patients with visible clots on CTA in a M3 branch of the middle cerebral artery were not included in the analysis because the CBS does not include M3 branches. Also, patients with a thrombus in the posterior circulation were not included because the CBS can only be applied in the anterior circulation. We assessed penumbra volume in the anterior circulation by first defining the total ischemic area as a relative measure of mean transit time (MTT) ≥145% compared with the contralateral (unaffected) hemisphere. Within the ischemic area, the infarct core is separated from the penumbra by an absolute threshold value of cerebral blood volume (CBV) < 2.0 ml/100 g. Penumbra volume, measured in mm^3, was divided into tertiles for analysis.[21]

In addition to our three main radiologic parameters of interest we evaluated the following other CT parameters that might be related to headache at stroke onset. On NCCT: presence of a hyperdense vessel sign, early CT signs of ischemia and the size of initial lesions in the anterior circulation measured by ASPECTS (Alberta Stroke Program Early CT Score). ASPECTS is a 10-point quantitative topographic score representing early ischemic change in the middle cerebral artery territory, with a normal scan receiving an ASPECTS of 10 points.[22, 23] For ASPECTS, both cortical and subcortical components were taken into account. ASPECTS scores were dichotomised at the median. On CTA source images (CTA-SI) we also assessed extent of ischemia using the ASPECTS, as well as presence and location of vascular occlusion. On CTP (CBV, MTT) we assessed the location and the volume of the infarct core and the penumbra.

Statistical analysis

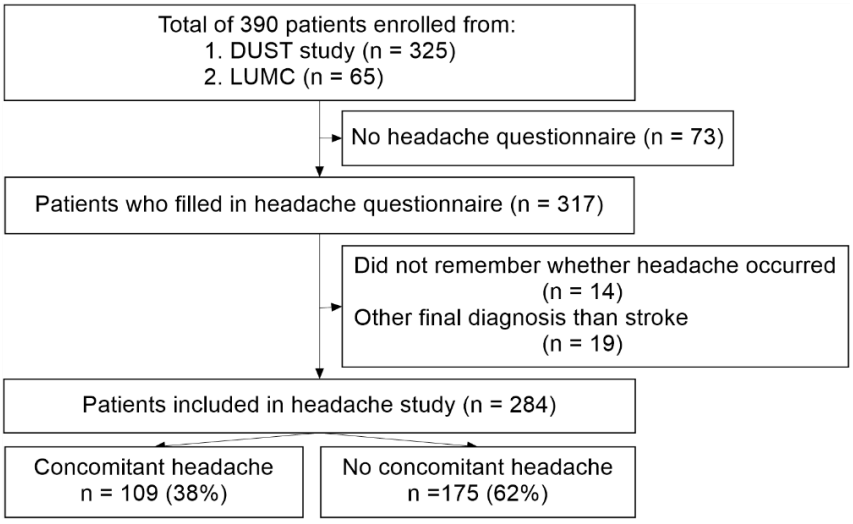
We performed univariable Poisson regression analyses to identify clinical and radiological parameters associated with headache at stroke presentation. Adjustments were made for possible confounders in multivariable Poisson regression analysis. For cerebral vessel atherosclerosis no adjustments were made for age and sex or other cardiovascular risk factors since these factors were considered to be intermediates in the causal pathway of the disease. For the clot burden score adjustments were made for age, sex and stroke-to-imaging time. For all other radiological characteristics except clot localisation on CTA, adjustments were made for stroke-to-imaging time. Risk ratios (RR) and adjusted RR (aRR) with 95% confidence intervals (CI) were calculated.

Results

Patients

In total 284 patients were included in this study (Figure 1). Of these patients, 109 (38%) experienced concomitant headache during the early phase of ischemic stroke. Mean age of all patients was 68 ± 13 (SD), median NIHSS was 4 and median stroke-to-imaging time was 131 minutes. Mean age, median NIHSS and median stroke-to-imaging time did not differ between patients with and patients without headache. The baseline characteristics are shown in Table 1. Headache was more common in patients without a history of hypertension and in patients with a history of migraine. Clinical follow up data were available of 273 patients. There were no differences in baseline characteristics in the patients with and without follow-up. Overall 71% of the patients had a good outcome (mRS ≤ 2).

Figure 1. Flowchart of patients



Radiological parameters

Table 3 shows headache prevalence in patients in presence or in absence of a specific radiological characteristic. Headache was less prevalent in patients with than in patients without atherosclerosis in the extracranial anterior circulation (35% versus 47%; RR: 0.72; 95% CI: 0.54–0.97). We found no relation between the presence of headache during the early phase of stroke and clinical outcome at three months follow up. Headache characteristics are shown in Table 2. In almost one third of the patients, headache preceded stroke onset.

The effect estimates of presence of extracranial atherosclerosis in the posterior circulation, presence of intracranial atherosclerosis and highest versus lowest tertile intracranial ICA calcification volume were all in the same direction with less headache prevalence, though these findings were not statistically significant. There was no difference in headache prevalence in patients with and patients without an observed clot (40% versus 39%; aRR: 1.00; 95% CI: 0.73–1.37). Clot burden score was assessed in the 82 patients (29%) with anterior circulation stroke confirmed on CTA. Headache prevalence in patients with large clot extent was not different from those with small clot extent (aRR: 1.02 for highest versus lowest tertile; 95% CI: 0.86–1.20).

Penumbra volume data were available for 110 patients. There was no difference in headache prevalence in patients with or without a perfusion defect (aRR: 0.98; 95% CI: 0.72–1.35). In addition, headache presence did not vary according to penumbra volume (RR: 1.08 for tertile with largest volume versus tertile with lowest volume; 95% CI 0.63–1.85). On NCCT, other radiological characteristics did not show any significant relation with headache at stroke onset, nor did infarct core volume on CTP. As assessed with CTA headache was more prevalent in patients with infarctions in the posterior circulation than in the anterior circulation (RR 1.78; 95% CI: 1.15–2.76).

Table 1. Baseline characteristics of the 284 participants according to presence or absence of concomitant headache

Clinical characteristics	% headache with characteristic: Present	Absent
Demographics		
Age under 50, n (%)*	15 (44%)	94 (38%)
Women, n (%)	49 (37%)	60 (39%)
History, n (%)		
Previous stroke or TIA	24 (40%)	83 (38%)
Hypertension	41 (29%)	67 (49%)
Diabetes mellitus	13 (34%)	95 (39%)
Hyperlipidemia	35 (37%)	71 (39%)
Myocardial infarction	11 (38%)	96 (39%)
Atrial fibrillation	15 (42%)	93 (38%)
Peripheral artery disease	4 (50%)	104 (38%)
Migraine	34 (51%)	74 (34%)
Smoking	72 (41%)	36 (36%)
Alcohol use	66 (45%)	34 (34%)
Bloodpressure on admission, n (%)		
Systolic BP > 160 mm Hg (±SD)	41 (37%)	67 (41%)
Diastolic BP > 90 mm Hg (±SD)	33 (34%)	75 (42%)
NIHSS ≥ 7 on admission, n (%)**	32 (36%)	73 (40%)
mRS ≤ 2 at 3-month follow up	70 (36%)	35 (44%)

**Dichotomization of age under 50 is used as a measure for young stroke*

***National Institutes of Health Stroke Scale, dichotomized at <7 and≥ 7*

Table 2. Headache characteristics of the 109 patients with headache based on semi-structured questionnaire

Question	n (%)	Question	n (%)
Headache onset		Nature of headache	
Before symptoms	34 (31%)	Pressure/ sore	72 (66%)
Simultaneous with symptoms	12 (11%)	Throbbing/ lancinating	18 (17%)
Seconds after symptoms	1 (1%)	Other	10 (9%)
Minutes after symptoms	11 (10%)	Unknown	9 (8%)
Hours after symptoms	37 (34%)	Headache duration	
Unknown	14 (13%)	Seconds	2 (2%)
Familiar with headache		Minutes	6 (5%)
This type	35 (32%)	Hours	29 (26%)
Other type	20 (18%)	Days	22 (20%)
None	49 (45%)	Still present*	44 (40%)
Unknown	5 (4%)	Unknown	6 (6%)
Headache location		Concomitant symptoms**	
Left side of head	9 (8%)	Photophobia	14 (13%)
Right side of head	17 (16%)	Phonophobia	9 (8%)
Occipital	10 (9%)	Nausea	19 (17%)
Anterior	23 (21%)	Vomiting	17 (16%)
Diffuse (entire head)	14 (13%)	Dizziness	25 (23%)
Like a band around head	12 (11%)	None	40 (37%)
Unknown	24 (22%)		

**'Still present' is defined as time difference in headache onset and time of collection of questionnaire, which is 2.5 days on average.*

***Patients can experience multiple symptoms, explaining the total percentage of over 100%*

Table 3. Radiological characteristics of the 284 participants according to presence or absence of concomitant headache

Radiological characteristics	% headache with characteristic: Present	Absent	RR (95%CI)	aRR (95%CI)
Main characteristics of interest				
Presence of extracranial atherosclerosis	72/204 (35%)	35/74 (47%)	0.75 (0.55–1.01)	x°
Anterior circulation	69/198 (35%)	39/81 (48%)	0.72 (0.54–0.97)	x°
Posterior circulation	39/101 (39%)	67/172 (39%)	0.99 (0.73–1.35)	x°
Presence of intracranial atherosclerosis	77/216 (36%)	30/62 (48%)	0.74 (0.54–1.01)	x°
ICAC volume (tertiles)				x°
T2 (medium ICA calcification volume)	34/84 (41%)	39/88 (44%)*	0.91 (0.64–1.30)	x°
T3 (high ICA calcification volume)	31/88 (35%)	39/88 (44%)*	0.80 (0.55–1.15)	x°
Clot burden score: presence of clot	43/108 (40%)	65/169 (39%)	1.04 (0.77–1.40)	1.00 (0.73–1.37)†
Clot burden score: clot extent (tertiles)				
T2 (medium clot extent)	9/25 (36%)	9/25 (36%)**	1.00 (0.85–1.18)	1.02 (0.87–1.20)†
T3 (large clot extent)	8/23 (35%)	9/25 (36%)**	1.01 (0.86–1.19)	1.02 (0.86–1.20)†
Presence of perfusion defect	55/142 (39%)	48/125 (38%)	1.01 (0.75–1.37)	0.98 (0.72–1.35)‡
Penumbra volume (tertiles)				
T2 (medium penumbra volume)	14/38 (37%)	15/36 (42%)***	0.88 (0.50–1.56)	0.87 (0.50–1.53)‡
T3 (large penumbra volume)	16/36 (44%)	15/36 (42%)***	1.07 (0.63–1.82)	1.08 (0.63–1.85)‡
Other characteristics				
Non-contrast CT				
Hyperdense vessel sign	16/40 (40%)	92/241 (38%)	1.05 (0.69–1.58)	1.08 (0.71–1.64)‡
Early CT sign	23/60 (38%)	69/177 (39%)	0.98 (0.68–1.42)	1.01 (0.69–1.48)‡
ASPECTS score < 9	13/25 (52%)	18/51 (35%)	1.47 (0.87–2.50)	1.32 (0.75–2.31)‡
CT angiography				
Detection ischemia (CTA-SI)	34/80 (43%)	74/198 (37%)	1.14 (0.83–1.55)	1.11 (0.80–1.55)‡
ASPECTS < 8	13/34 (38%)	22/55 (40%)	0.96 (0.56–1.63)	0.95 (0.56–1.61)‡
Posterior circulation localization	15/25 (60%)	28/83 (34%)	1.78 (1.15–2.76)	x°
Infarct core volume (tertiles)				
T2 (medium volume)	15/37 (41%)	14/36 (39%)*4	1.04 (0.59–1.85)	1.02 (0.58–1.79)‡
T3 (high volume)	16/37 (43%)	14/36 (39%)*4	1.14 (0.64–2.02)	1.09 (0.63–1.88)‡

ICA: internal carotid artery. ASPECTS: Alberta Stroke Progam Early CT Score. CTA-SI: CT angiography, source images

†Adjusted for age, sex and stroke-to-imaging time. ‡Adjusted for stroke-to-imaging time. °Adjustments not desirable

**headache prevalence in T1 (small or no ICA calcification volume). **headache prevalence in T1 (small clot extent)*

****headache prevalence in T1 (small penumbra volume). *4 headache prevalence in T1 (small infarct core volume).*

Discussion

We found that headache during the early phase of ischemic stroke is less common in patients with extracranial carotid atherosclerosis. Also, less headache was present in patients with atherosclerosis in the extracranial posterior or intracranial circulation although this difference was not statistically significant. However, clot extent and penumbra volume were not associated with headache during ischemic stroke.

The mechanisms for headache during the early phase of ischemic stroke are not well understood. Our data suggest that vessel wall integrity and elasticity might be important factors, possibly facilitating the activation of perivascular nerve fibers leading to headache.[7, 24, 25] Since the posterior circulation has a denser perivascular innervation, this hypothesis might explain why headache is relatively more common in patients with infarctions in the posterior circulation.[26] Our findings do not provide support for the hypotheses that headache can be elicited by direct compression of the vessel wall by a large blood clot or by activation by peri-infarct core SDs of perivascular sensory trigeminal afferents.[27] No relation was found between increasing penumbra volume as proxy for presence of SDs and prevalence of concomitant headache. It should be noted, however, that we could not assess the penumbra of the posterior circulation in our study. This study confirms previously reported associations of ischemic-stroke associated headache and posterior circulation infarcts or a history of hypertension or migraine.[3, 7] In contrast to other studies[5, 7] we failed to find associations between ischemic-stroke associated headache and female sex, young age, or clinical outcome. In line with previous studies, the headache was pressing in 66% and throbbing in 17% and preceded stroke onset in nearly one third of patients. Pre-stroke headache had no specific characteristics and time between headache onset and stroke symptom onset varied from seconds to several days. Its mechanism is puzzling.

Our study also has limitations. Not all radiological parameters could be assessed in all patients. Intracranial internal carotid artery calcium (ICA) calcification volume, clot burden score, and ASPECTS scores can by definition only be assessed in the anterior circulation. Penumbra and infarct core volume could only be assessed in the anterior circulation because of lack of validated thresholds for the posterior circulation. Additionally, penumbra and infarct core are defined by relative mean transient time measurements for which comparison with a healthy hemisphere is needed, whereas posterior circulation infarctions are often bilateral. CTP in general is software dependent. Since thresholds for defining infarct core and penumbra are uncertain, quantification bears uncertainty as well. Additionally, we used the arbitrary threshold of 160 Hounsfield units to assess the intracranial ICA

calcification volumes. This does not correspond with the threshold of 130 Hounsfield units reported in the literature, though this threshold was derived from the Agatston score for coronary artery calcifications.[28, 29] We based our 160 Hounsfield units on optimal distinction between intracranial ICA calcifications and skull base in data from all different vendors, variation of calcification volume data did not differ notably between centers. Finally, as participants had to be able to answer the headache questionnaire, patients with a severe disease course were not included. This might affect the generalizability of the results to this group of patients. In 73 patients the headache questionnaire was not filled in. This was mainly because of logistic reasons and the baseline characteristics of these patients were not different from the participants. Fourteen patients (5%) did not remember whether they had headache at stroke onset. These patients had more often severe strokes and were more often aphasic than patients who were included in the study. However, because of the small number of patients the influence of this possible source of selection bias is likely to be small.

Strong points of our study include the large number of participants, prospective assessment of the headache, and use of state-of-the-art imaging methods enabling detailed assessment of the radiological characteristics of interest. With emerging novel imaging techniques such as arterial spin labeling with MR[30, 31], we might be able in the near future to assess perfusion of the posterior circulation as well. This would certainly facilitate the deciphering of the pathophysiological mechanisms of acute ischemic stroke-associated headache.

References

1. Verdelho A, Ferro JM, Melo T, Canhao P, Falcao F. Headache in acute stroke. A prospective study in the first 8 days. *Cephalalgia*. 2008;28:346-354
2. Abadie V, Jacquin A, Daubail B, et al. Prevalence and prognostic value of headache on early mortality in acute stroke: The dijon stroke registry. *Cephalalgia*. 2014
3. Kropp P, Holzhausen M, Kolodny E, et al. Headache as a symptom at stroke onset in 4,431 young ischaemic stroke patients. Results from the "stroke in young fabry patients (sifap1) study". *J. Neural Transm.* 2013;120:1433-1440
4. Maino A, Algra A, Koudstaal PJ, et al. Concomitant headache influences long-term prognosis after acute cerebral ischemia of noncardioembolic origin. *Stroke*. 2013;44:2446-2450
5. Tentschert S, Wimmer R, Greisenegger S, Lang W, Lalouschek W. Headache at stroke onset in 2196 patients with ischemic stroke or transient ischemic attack. *Stroke*. 2005;36:e1-3
6. Evans RW, Mitsias PD. Headache at onset of acute cerebral ischemia. *Headache*. 2009;49:902-908
7. Mitsias PD, Ramadan NM, Levine SR, Schultz L, Welch KM. Factors determining headache at onset of acute ischemic stroke. *Cephalalgia*. 2006;26:150-157
8. Abou-Chebl A, Krieger DW, Bajzer CT, Yadav JS. Intracranial angioplasty and stenting in the awake patient. *J. Neuroimaging*. 2006;16:216-223
9. John N, Mitchell P, Dowling R, Yan B. Is general anaesthesia preferable to conscious sedation in the treatment of acute ischaemic stroke with intra-arterial mechanical thrombectomy? A review of the literature. *Neuroradiology*. 2013;55:93-100
10. Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ. Clinical relevance of cortical spreading depression in neurological disorders: Migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J. Cereb. Blood Flow Metab.* 2011;31:17-35
11. Dreier JP, Major S, Manning A, et al. Cortical spreading ischaemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid haemorrhage. *Brain*. 2009;132:1866-1881
12. Noseda R, Burstein R. Migraine pathophysiology: Anatomy of the trigeminovascular pathway and associated neurological symptoms, csd, sensitization and modulation of pain. *Pain*. 2013;154 Suppl 1

13. Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. *Nat. Med.* 2011;17:439-447
14. Shatillo A, Koroleva K, Giniatullina R, et al. Cortical spreading depression induces oxidative stress in the trigeminal nociceptive system. *Neuroscience*. 2013;253:341-349
15. van Seeters T, Biessels GJ, van der Schaaf IC, et al. Prediction of outcome in patients with suspected acute ischaemic stroke with ct perfusion and ct angiography: The dutch acute stroke trial (dust) study protocol. *BMC Neurol.* 2014;14:37
16. Horsch AD, Dankbaar JW, van der Graaf Y, et al. Relation between reperfusion and hemorrhagic transformation in acute ischemic stroke. *Neuroradiology*. 2015
17. Niesten JM, van der Schaaf IC, Biessels GJ, et al. Relationship between thrombus attenuation and different stroke subtypes. *Neuroradiology*. 2013;55:1071-1079
18. van der Hoeven EJ, Dankbaar JW, Algra A, et al. Additional diagnostic value of computed tomography perfusion for detection of acute ischemic stroke in the posterior circulation. *Stroke*. 2015;46:1113-1115
19. Doherty TM, Asotra K, Fitzpatrick LA, et al. Calcification in atherosclerosis: Bone biology and chronic inflammation at the arterial crossroads. *Proc. Natl. Acad. Sci. U. S. A.* 2003;100:11201-11206
20. Tan IY, Demchuk AM, Hopyan J, et al. Ct angiography clot burden score and collateral score: Correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am. J. Neuroradiol.* 2009;30:525-531
21. Wintermark M, Flanders AE, Velthuis B, et al. Perfusion-ct assessment of infarct core and penumbra: Receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke*. 2006;37:979-985
22. Pexman JH, Barber PA, Hill MD, et al. Use of the alberta stroke program early ct score (aspects) for assessing ct scans in patients with acute stroke. *AJNR Am. J. Neuroradiol.* 2001;22:1534-1542
23. Wardlaw JM, Mielke O. Early signs of brain infarction at ct: Observer reliability and outcome after thrombolytic treatment--systematic review. *Radiology*. 2005;235:444-453
24. Mitsias P, Ramadan NM. Headache in ischemic cerebrovascular disease. Part ii: Mechanisms and predictive value. *Cephalalgia*. 1992;12:341-344
25. Arboix A, Massons J, Oliveres M, Arribas MP, Titus F. Headache in acute cerebrovascular disease: A prospective clinical study in 240 patients. *Cephalalgia*. 1994;14:37-40

26. Libman RB, Kwiatkowski TG, Hansen MD, Clarke WR, Woolson RF, Adams HP. Differences between anterior and posterior circulation stroke in toast. *Cerebrovasc. Dis.* 2001;11:311-316
27. Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat. Med.* 2002;8:136-142
28. Bos D, van der Rijk MJ, Geeraedts TE, et al. Intracranial carotid artery atherosclerosis: Prevalence and risk factors in the general population. *Stroke*. 2012;43:1878-1884
29. Odink AE, van der Lugt A, Hofman A, et al. Association between calcification in the coronary arteries, aortic arch and carotid arteries: The rotterdam study. *Atherosclerosis*. 2007;193:408-413
30. Hu LB, Hong N, Zhu WZ. Quantitative measurement of cerebral perfusion with intravoxel incoherent motion in acute ischemia stroke: Initial clinical experience. *Chin. Med. J. (Engl.)*. 2015;128:2565-2569
31. Majer M, Mejdoubi M, Schertz M, Colombani S, Arrigo A. Raw arterial spin labeling data can help identify arterial occlusion in acute ischemic stroke. *Stroke*. 2015;46:e141-144