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Headache Attributed to Acute Ischemic Stroke in Chinese Patients: A Single Center Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author XC designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors HS and ZC managed the analyses of the study. Author MZ managed the literature searches. Author SY designed the study and revised it for intellectual content. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aims: In this pilot study we aimed to investigate prevalence, characteristics and possible mechanisms of headache in acute ischemic stroke from a Chinese tertiary hospital.
Methodology: Five hundred and fifteen patients with acute ischemic stroke from Chinese PLA General Hospital were retrospectively investigated. Headache prevalence, features and correlations with several clinical parameters (age, sex, vascular risk factors, atherosclerosis, artery stenosis, infarct locations, presumed etiology according to TOAST criteria) were analyzed.
Results: Of 515 participants, 36 (7%) experienced headache during the acute event. Younger age, non-atherosclerosis and occipital lobe infarct were more associated with headache occurrence ($P<0.05$). Headache occurred mostly within one day before (41.7%) or simultaneously (47.2%) with other ischemic symptoms in a stroke. Most patients had tension-like headache. There is no significant correlation of headache location with infarct location.
Conclusion: Our study indicated that non-atherosclerosis cerebrovascular diseases and

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cortical spreading depression caused by occipital infarction might play a role in stroke onset headache. Headache may be a warning sign of stroke onset since most headaches occurred shortly before or simultaneously with stroke. Headache information needs to be fully recorded in prospective stroke registry.

Keywords: Headache; acute ischemic stroke; prevalence; clinical correlation.

ABBREVIATIONS

TIA : Transient Ischemic Attack;
PLA : People's Liberation Army;
MRI : Magnetic Resonance Imaging;
CT : Computed Tomography;
ICHD-3β : International Classification of Headache Disorders-3beta;
CTA : Computerized Tomographic Angiography;
MRA : Magnetic Resonance Angiography;
VAS : Visual Analogue Scale.

1. INTRODUCTION

Headache was considered as a common symptom accompanying acute ischemic cerebrovascular diseases in the western countries. The prevalence of headache was reported to be 8-38% in acute ischemic stroke and 16-36% in transient ischemic attack (TIA) 1-4]. But in a large-scale study of Taiwan Stroke Registry, only 7.4% patients had stroke-onset headache during first-ever ischemic stroke 5]. The prevalence of headache in acute ischemic stroke was unknown in China mainland. The mechanisms by which an acute ischemic stroke results in headache were poorly understood. The occurence of headache at stroke onset may be associated with younger age, female, better vascular elasticity, posterior circulation infarction, and infarct in pain processing regions 35,6]. This study was undertaken to assess headache characteristics and related factors in acute ischemic stroke patients who were consecutively admitted to a Chinese tertiary hospital.

2. METHODOLOGY

2.1 Participants

We conducted this study in Chinese PLA General Hospital (301 Hospital), a big tertiary hospital in the north of China and the study was approved by Institutional Review Board. We retrospectively collected data of patients who were discharged from Department of neurology and finally diagnosed as “cerebral infarction” between January 1, 2017 and May 31, 2017 from the hospital workstation. Inclusion criteria were as follows: 1) age ＞18 years; 2) onset of stroke symptoms ＜ 14 days at hospitalization;3) headache occurred within 3 days before stroke onset or within 7 days after stroke; 4) Diagnostic criteria for headache attributed to ischemic stroke (cerebral infarction) referred to code 6.1.1 in the International Classification of Headache Disorders-3β (ICHD-3β), which defined that headache had developed in very close temporal relation to other symptoms and/or clinical signs of ischemic stroke and/or significantly improved in parallel with stabilization or improvement of other symptoms or clinical or radiological signs of ischemic stroke 10]; 5) all the patients had brain magnetic resonance imaging (MRI) or computed tomography (CT) scanning. We excluded TIA, intracerebral hemorrhage, stroke secondary to cerebral venous thrombosis or intracranial tumors, and stroke onset ＞ 14 days at hospitalization.

We recorded demographic information, risk factors, migraine history, infarct location, circulation division, whether atherosclerosis existing by ultrasound/ computerized tomographic angiography (CTA) or magnetic resonance angiography (MRA) exam, whether intracranial or cervical arteries being narrowed, presumed etiology by TOAST classification 11], headache characteristics (location, features, extent using visual analogue scale(VAS), duration, headache onset time).

2.2 Statistics

Statistical analyses were carried out using SPSS 22.0. Two sample t-tests were used for continuous variables. X2 tests were used for binary and categorical variables. Stepwise logistic regression was done to assess the relation between clinical variables and headache occurring around stroke attack. All variables which were at least weakly associated with headache at stroke onset were included (P<0.25

in univariate analyses). P values of ＜0.05 were considered significant.

3. RESULTS AND DISCUSSION

3.1 Results

We retrieved 602 patients who were finally diagnosed as “cerebral infarction” in our workstation. Eighty-seven patients were excluded according to exclusion criteria, and 515 patients with acute ischemic stroke met our inclusion criteria (Fig. 1).

3.1.1 Acute ischemic stroke with or without headache

Table 1 demonstrated demographic and clinical information of the included patients. All the patients came from China mainland covering 22 provinces. Of the 515 included patients, 502 (97.5%) had MRI confirmed new infarction and 13(2.5%) had CT scanning because of contraindication for MRI due to heart pacemakers or other metal substances in the bodies. Forty-eight (9.3%) patients had disturbance of consciousness and 12(2.3%) had complete aphasia. Headache around stroke onset was recorded in 36(7%) patients in our study. Fourteen (8.8%) of 159 females and 22(6.2%) of 356 males had headache. Sex constitution made no significant difference between patients with or without headache (P=0.280). Patients with headache were much younger than without headache (Mean age: 54.9±14.0 VS 63.7±13.8 years, P < 0.001).

There were no significant differences of headache prevalence regarding infarct side, circulation division, infarct regions, TOAST subtypes, frequency of intracranial or extracranial artery stenosis. However, headache tended to occur more frequently in stroke of other cause (10.8%) and undetermined cause (18.2%), in posterior circulation (9.8%) than anterior circulation (5.9%) infarct, especially in cerebellar infarct (15.8%), in right-side (9.0%) than left-side (4.8%) infarct. This side difference was restricted to the anterior circulation infarct (Table 1 and 2). Headache was more frequently present when occipital lobe was involved in a stroke than not involved (22.6% VS 5.2%, P < 0.001). Headache was significantly less frequently reported in patients with than without atherosclerosis (5.7% VS 12.0%, P=0.022) which was detected by ultrasound and/or CTA or MRA. All variables with a P-value < 0.25 were included as potential candidates in the stepwise logistic regression procedure. These variables included age, infarct laterality, occipital involvement, atherosclerosis, intracranial artery stenosis, and extracranial artery stenosis. Regression analysis indicated that age younger than 40 years (P=0.024, OR 8.433, 95%CL1.318, 53.965) and occipital involvement (P=0.000, OR 7.042, 95%CL3.106,

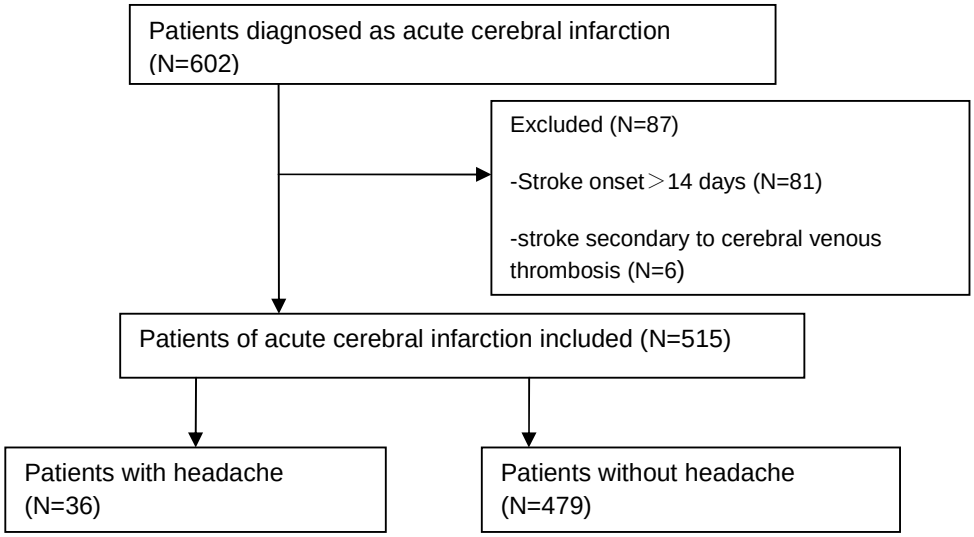

Fig. 1. Flow chart

Table 1. Clinical feature of acute ischemic stroke(with or without headache)

Items		Headache N=36(%)	No Headache N=479	Total N=515	P Value
Sex	Male	22(6.2%)	334	356	0.280
	Female	14(8.8%)	145	159	
Age		54.9(14.0)	63.7(13.8)		＜0.001*
Hypertension	Yes	26(7.5%)	319	345	0.489
	No	10(5.9%)	160	170	
Diabetes	Yes	10(5.4%)	174	184	0.302
	No	26(7.9%)	305	331	
Atrial Fibrillation	Yes	1(3.4%)	28	29	0.441
	No	35(7.2%)	451	486	
Circulation division	Ant. circulation	20(5.9%)	319	339	0.303
	Post. circulation	14(9.8%)	129	149	
	Both	2(6.1%)	31	33	
Infarct side	left	11(4.8%)	218	229	0.204
	right	20(9.0%)	201	221	
	Bilateral	5(7.7%)	60	65	
Infarct location	Cortex	10(8.1%)	113	123	0.451
	Subcortex or BG	9(5.4%)	158	167	
	Multiple infarct	11(8.4%)	120	131	
	Cerebellum	3(15.8%)	16	19	
	Brain stem	2(3.4%)	56	58	
	Thalamus	1(5.9%)	16	17	
Occipital involvement	Yes	12(22.6%)	41	53	＜0.001*
	No	24(5.2%)	437	461	
TOAST classification	Large-artery Atherosclerosis	20(7.5%)	247	267	0.362
	Small-artery occlusion	8(5.3%)	144	152	
	Cardioembolism	2(4.2%)	46	48	
	Other cause	4(10.8%)	33	37	
	Undetermined cause	2(18.2%)	9	11	
Atherosclerosis	Yes	23(5.7%)	382	405	0.022*
	No	13(12.0%)	95	108	
Extracranial artery stenosis	Yes	12(9.2%)	118	130	0.208
	No	23(6.0%)	360	383	
Intracranial artery stenosis	Yes	15(8.4%)	163	178	0.201
	No	18(5.5%)	310	328	
Total		36(7.0%)	479	515	

**:<0.05; BG: basal ganglion; Ant.: anterior; Post.: posterior*

15.873). were the factors independently associated with headache occurrence around stroke onset.

No patients with headache in acute ischemic stroke had a history of migraine or other types of headache according to the records of past history. The frequency of hypertension, diabetes mellitus or glucose intolerance, atrial fibrillation was of no difference between patients with or without headache.

3.1.2 Characteristics of headache attributed to ischemic stroke

Table 2 demonstrated clinical characteristics of patients with headache attributed to ischemic stroke. Of the 36 patients who had stroke related headache, 16(41.7%) had headache between 1 hour to 1 day prior to onset of other ischemic symptoms in a stroke, 17(47.2%) had headache simultaneously with other ischemic symptoms. Two (5.6%) patients with large-area infarct even

after thrombolysis had headache within 72 hours after stroke. Two (5.6%) patients had headache 72 hours after stroke, one of whom had hemorrhagic transformation while headache occurred, and one had severe intracranial artery stenosis. Headache always disappeared after several days of treatment for infarction. As headache information was not recorded daily, accurate headache duration was not available. Headache extent was evaluated using VAS for only 6 patients with average score of 4.7±1.5. Most patients (16/36,42.1%) were described as non-throbbing headache and only 6(15.8%) were recorded as throbbing headache, while headache feature was not described in 15 (39.5%) patients.

The location of headache was frontal in 12(33.3%) and posterior in 4 (11.1%) patients. Headache location was not described in 14 (38.9%) patients. Headache was frontal in anterior circulation infarct and in occipital region or neck with posterior circulation infarct in 12(33.3%) patients. Three (8.3%) patients with both anterior and posterior circulation infarct had headache located in both ipsilateral anterior and posterior region of head. However, 4(11.1%) patients presented as frontal headache with posterior circulation infarct and 1(2.8%) patient presented as posterior headache with anterior circulation infarct. Two (5.6%) patients presented as whole-brain headache with one side of anterior circulation infarct. Headache location was ipsilateral to infarct side in 13 patients (36.1%). Six (15.8%) had one-side infarct but bilateral headache. Two (5.6%) had bilateral infarct and bilateral headache. One (2.8%) had bilateral infarct but headache at one side. There is no significant correlation of headache location with infarct side (P=0.341) or circulation distribution (P=0.298).

3.2 Discussion

This pilot study was the first study in China mainland to investigate the prevalence and characteristics of ischemic stroke related headache. Only 7% patients reported headache. The prevalence of headache in our study was similar to that of a Taiwan stroke registry (7.4% had onset headache) 5], relatively lower than those of other countries or areas 1]. This may be related to the following factors: 1) Patients' perception threshold to pain was different

Table 2. Characteristics of patients with stroke related headache

Items		Ant.C N=20	Post.C N=14	Both N=2	Total, N=36	P Value
Sex	Male	11	9	2	22(61.1%)	0.128
	Female	9	5	0	14(38.9%)	
Infarct side	Left	5	6	0	11(30.6%)	<0.001
	Right	15	6	0	21(58.3%)	
	Bilateral	0	2	2	4(11.1%)	
TOAST classification	Large-artery atherosclerosis	10	9	1	20(55.6%)	0.121
	Small-artery occlusion	5	2	0	7(19.4%)	
	Cardioembolism	2	0	0	2(5.6%)	
	Other cause	1	2	1	4(11.1%)	
	Undetermined cause	2	1	0	3(8.3%)	
Headache and infarct laterality	Ipsilateral	8	4	1	13(36.1%)	0.731
	Unclear	8	6	0	14(38.9%)	
	Bilateral headache	4	4	1	9(25.0%)	
Anterior and posterior division of headache and infarct	Consistent	6	4	2	12(33.3%)	0.422
	Inconsistent	2	3	0	5(13.9%)	
	Both anterior and posterior headache	4	1	0	5(13.9%)	
	Unclear	8	6	0	14(38.9%)	
Onset time of headache	Prior to stroke	7	7	1	15(41.7%)	0.588
	Simultaneous	10	6	1	17(47.2%)	
	Within 72h after stroke	2	0	0	2(5.6%)	
	After 72h after stroke	1	1	0	2(5.6%)	

Ant.C: anterior circulation; Post.C: posterior circulation

because of ethnic differences as both China mainland and Taiwan located in east Asia. 2) Headache history recording was inadequate as patients might pay more attention to speech or motor/sensory problems and ignore slight headache while doctors might also neglect to ask about headache information. 3) Some patients were unable to provide headache information because of aphasia or conscious disturbance. Some prospective studies in literature excluded these patients. Therefore, in order to acquire more accurate headache information in stroke, prospective well designed registry of stroke and headache is necessary.

The mechanisms of headache in acute ischemic stroke are poorly understood. Injury to pain-sensitive arteries 12], dilation of pain-sensitive collateral vasculature 13], electrochemical or mechanical stimulation of the trigeminovascular afferent system and central pain matrix areas 1,7] are possible mechanisms.

Similar to several previous reports, headache related to ischemic stroke in our study occurred more often in younger patients [3,614-16] and patients with no atherosclerosis 2]. Some studies showed that absence of hypertension history was one of the independent predictors of headache in stroke, and could indirectly suggest that atherosclerosis play a less important role in the pathogenesis of stroke with headache 417]. Preserved elasticity and activation of dense perivascular afferent nerves was considered as a significant factor leading to the development of onset headache 17]. On the other hand, younger age and no atherosclerosis may reflect other or unknown vascular disorders (arterial dissection, Moyamoya disease, vasculitis, fibromuscular dysplasia, embolism of unknown source, etc) in the role of stroke related headache. For in our study, headache was more frequent in ischemic stroke of other cause (10.8%) or unknown cause (18.2%) by TOAST classification although not reaching statistic significance. Arterial dissection, as an important cause of stroke, headache and neck pain 12], however, was not found in headache patients but in 3 patients without headache in this study.

Posterior circulation infarct was reported to be more associated with headache in some studies [3,6,14,18-19]. A denser perivascular innervation of posterior circulation vessels 20], ischemia of the trigeminal nucleus or the serotoninergic nuclei of the brainstem 211,22], or even ischemia of the dura partially supplied by the posterior cerebral artery 23] were potential mechanisms in headache production. One report indicated that association of headache with vertebrobasilar stroke was mainly because of its association with cerebellar stroke 16]. We also found a relatively higher prevalence of headache in cerebellar stroke (15.8%). Cerebellum was shown to be functionally connected with pain processing structures in trigeminal nociception 24]. Furthermore, we found stroke with occipital lobe involvement was significantly more associated with headache than without occipital involvement ((P $<$ 0.001). Cortical spreading depression (CSD) was considered a mechanism for migraine aura usually initiating from occipital lobe and may activate or sensitize pain-signaling pathways 25]. CSD was also found in ischemic stroke and can increase the infarct lesion size 26,27]. A study from our epileptic center also found a significantly higher incidence of postictal headache in occipital lobe epilepsy than frontal and temporal lobe epilepsy 28]. Therefore, headache in occipital lobe lesion may be well related to CSD.

In our study, headache was reported more frequently in ischemia of right carotid territory than that of left, which may be due to reporting bias because left hemispheric infarct can cause aphasia. However, another study found the same difference after excluding patients with language disturbances in left-hemispheric stroke, indicating other mechanisms apart from reporting bias may contribute to this left-and-right hemispheric difference 16].

In line with previous studies 30], most headache occurred within one day before or simultaneously with stroke onset, indicating that headache may serve as a warning sign of ischemic stroke. Fewer patients may have headache after stroke onset due to recurred large-area infarction or other reasons. The stroke-related headache was reported to last 3.8 days by average 31]. Definite headache duration was not available in our study because of incomplete recording. The onset time and duration of headache indicated other mechanisms rather than mechanical stimulation of edema to peri-infarct tissue led to stroke related headache. Blood pressure information was inadequate at headache onset in many patients, therefore, the role of blood pressure in headache was unknown. One study found that headache itself was closely associated with severe systolic blood pressure elevation (> or =

200 mmHg) in acute ischemic stroke indicating severely elevated blood pressure may be a cause of stroke onset headache 32].

Headache location was ipsilateral to infarct or generalized. Headache was generally frontal in the anterior circulation infarction and occipital in posterior circulation infarction, but may also be opposite or both frontal and occipital. In consistence with previous studies, the headache location cannot accurately predict the location of the ischemic event or the affected vessels 29]. The vessels of the circle of Willis and the supratentorial dura matter are mainly supplied by the trigeminal nerves, whereas the vascular structures of the posterior fossa are supplied by the upper cervical nerves, as well as the vagus and the trigeminal nerve 34]. The complicity of the nervous division may contribute to the discordance of headache location and infarct location or affected vessels.

There are some limitations in this retrospective study. Headache information was not fully recorded in a number of patients. Headache prevalence may be underestimated. Past headache history may be inaccurate due to recording bias. Associations of headache with severity and prognosis of stroke were not evaluated. However, this study can somewhat provide some information of headache in acute ischemic stroke in a part of Chinese population. As headache is a common symptom usually prior to or simultaneous with stroke onset, we call on researchers to pay more attention to headache attributed to ischemic stroke and to add headache information in prospective stroke registry. Stroke etiology and pathogenesis should be cautiously explored apart from atherosclerosis when headache is present because headache occurred more in patients with non-atherosclerosis. Further mechanisms of headache in acute ischemic stroke need to be explored.

4. CONCLUSION

In this study, prevalence of headache in acute ischemic stroke was relatively lower than that in most literature but similar to a Taiwan study. Non-atherosclerosis vascular diseases and cortical spreading depression (CSD) might play a role in ischemic stroke related headache. Headache may be a warning sign of stroke onset since 41.7% headaches occurred shortly before stroke and 47.2% simultaneously with stroke. We suggest headache experts and stroke experts should coordinate to improve headache information recording in future stroke registry and further explore possible mechanisms.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval was obtained from the ethics committee of the local institutional review board.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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