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Prospective Characterizations of Persistent Headache Attributed to Past Stroke

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Abstract

Background: Persistent Headache Attributed to Past Stroke (PHAPS) is a controversial entity, recently included in the new ICHD-3 classification despite being described only in retrospective studies. The aim of this study was to determine the incidence and characteristics of PHAPS in patients admitted with acute stroke.

Methods: We selected all patients with Headache Associated with Acute Stroke (HAAS) from a prospective, single-centre registry of patients with acute stroke admitted to a Neurology ward between November 2018 and December 2019. We analysed demographic, clinical and neuroimaging data. We assessed the follow-up with a phone call questionnaire at 6-12 months.

Findings: Among 121 patients with acute stroke, only 29 patients (24, 0%) had HAAS. From these, 6 were lost to follow-up. Twenty-three patients answered the 6 to 12-month follow-up questionnaire and were included in this study. Median age was 53 years (IIQ 38-78) and there was no gender predominance. Of the 10 patients (43, 5%) that had persistent headache, 8 clearly suffered from Previous Chronic Headaches (PCH), however, they all mentioned a different kind of headache. Only 1 patient did not have other reasons for a secondary headache.

Conclusions: In this study, only 10 out of 121 stroke patients (8.3%) referred persistent headache at the 6 to 12-month follow-up, and the majority already suffered from PCH. In patients with PCH we observed a change of the usual headache pattern with even total remission. Only one (<0, 1%) patient with persistent headache at the 6 to 12-month follow-up did not have a clear PCH history.

Keywords: Persistent headache attributed to past stroke; Secondary headache; Post-stroke pain

Introduction

Stroke is a very common diagnosis with an incidence of 1.9% in general population and reaching 14.1% in the age group between 65-74 years old [1,2]. Headache is a very frequent symptom, with an incidence of 50% a year in the general population, which is why there is an important overlap of these two entities by mere chance [1,2]. The mechanisms behind headache development in stroke involve compression of pain-sensitive structure like meninges and intracranial arteries which does not explain the majority of cases [3]. Other hypotheses concern cortical spreading depression triggered by ischemia with trigeminovascular activation behind cortical infarcts, the dense trigeminovascular innervation explaining the more prevalence of headache in posterior circulation strokes and also other theories related to lesion of structures involved in pain processing as well as release of inflammatory substances [4-6].

Persistent Headache Attributed to Past Stroke (PHAPS) is still a controversial clinical entity with an incidence reported in the literature between 10%-20% [6-9]. It is defined by the ICHD-3 classification as a headache fulfilling criteria for Acute Headache Associated with Stroke (HAAS) that persists past after stabilization of the ischemic event [10]. Previous studies revealed prevalence of headache following stroke between 10.8%-23.3% and new headache following stroke in the range of 12% [6-8; 11,12]. However, the majority of those clinical studies are retrospective with several limitations such as not discerning which patients had an history of Primary Chronic Headache (PCH), not evaluating iatrogenic causes for new onset headaches, not assessing pain medication overuse or even not having an imaging confirmation of stroke in the acute phase [6-8;11,12]. The pathophysiology behind this presumed entity is still vaguer than acute headache associated with stroke [3].

The aim of this study was to characterise and determine the incidence of Persistent Post Stroke Headache (PHAPS) in a population of stroke patients admitted to a Neurology ward, accounting multiple possible confounders. Our main hypothesis was that the persistence of headache following stroke might occur merely as manifestation of an already known previous chronic headache.

Methods

Study design

This was a single center and prospective study. Enrolled patients or their surrogates provided written informed consent.

We estimated that 110 patients would be needed to address the primary objective, assuming an adherence of 90% to phone calls and 20% prevalence of headache following stroke,

considering a significance level of 8% (two-sided) and a statistical power of 95%.

The study was conducted in accordance with the Declaration of Helsinki.

Patients

We selected all patients with Headache Associated with Acute Stroke (HAAS) from a prospective, single-centre registry of patients with acute stroke admitted to a Neurology ward between November 2018 and December 2019

All patients admitted to the Neurology ward with suspected ischemic or hemorrhagic stroke were eligible for inclusion if they had a confirmed stroke by imaging method (either CT scan or magnetic resonance imaging). Other inclusion criteria were an age of 18 years or older and a 24-hour gap between the headache development and focal symptoms (or headache alone with confirmed stroke by imaging method in 24 hours).

Patients with communication problems (aphasia, dementia, altered consciousness, severe dysarthria), anosognosia, lack of consent, negative imaging, pregnancy or incomplete questionnaires were excluded.

In the first days of admission, a standard questionnaire addressing headache characteristics was conducted to all patients who had a stroke suspicion. Patient's comorbidities were extracted based on electronic registries and standard questionnaires. Important information regarding possible confounding factors for headache were included in the questionnaires.

Stroke aetiology, for ischemic events, was determined i agreement with the Trial of Org 10172 in Acute Strok Treatment (TOAST) classification.

Questionnaires addressing possible confounders wer conducted for depression (PHQ-9), sleep apnoea (Epworth) an headache impact on daily activities (HIT-6). Other possibl confounders were analysed: coffee/tea consumption, weight gain, pain medication overuse and regular medication changes following stroke.

The intensity of headache was classified as mild if the patients scored 3 or below on the Numeric Rating Scale (NRS), moderate with a score between 4 and 7, and severe with a score of 8 or higher.

Headache was classified as probable migraine (G43.83) or probable tension-type headache (G.44.28), using the criteria from the third edition of The International Headache Classification (ICHD-3). Patients presenting both with "probable migraine" and "probable tension-type" headache were classified as "mixed" headache. Patients who could not be classified as probable migraine, tension-type or mixed headache were categorized as having "other" headache.

Follow-up

All patients with HAAS were reached out by telephone or e-mail (when available) at 6 months to a year post discharge. Several phone calls were made and patients with 5 missed calls at different times and different days were excluded.

Statstcal analysis

Patients were divided in two groups for statistical purposes, the ones which remained with headache at the follow-up questionnaire, and the ones which ceased the headache complaints by that time. Populations were compared for medical comorbidities (including previous chronic headache history), body mass index, smoking/ alcohol history, stroke aetiology, stroke localization, NIHSS, medication (including calcium channel blockers and dipyridamole), PHQ-9 and Epworth scores. Data were analysed with SPSS® v. 23 software. Pearson's x2 test or Fisher's exact test was conducted for comparison of categorical variables depending on group sizes. T-test and Wilcoxon rank-sum were applied for continuous variables. Odds Ratio (OR) was used to estimate risk factors for developing persistent headache. Two-tailed probability (p) values <0.05 were considered significant.

Results

During the study period, 276 patients were evaluated for inclusion. Several patients were excluded according to the study methods (Figure 1). Among 121 patients with acute stroke from the registry, 29 (24, 0%) had Headache Associated with Acute Stroke (HAAS). From these, 23 patients answered the 3-month follow-up questionnaire and were included in this study.

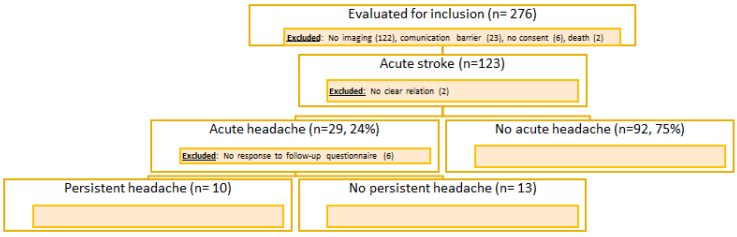

Figure 1: Study flow chart.

At the follow-up, both groups were similar in demographic factors and clinical comorbidities. Median age was 53 years (IIQ 38-78) and there was no gender predominance (Table 1).

	Persistent headache	No persistent headache	p value
Females (n, %)	5 (50, 0%)	4 (30, 8%)	0,417
Age (years)			0,852
Median (IIQ)	53 (38, 78%)	55 (49, 65%)	
Body mass index			0,804
Median (IIQ)	29 (24, 31%)	25 (23.32%)	
Hypertension (n, %)	7 (70, 0%)	9 (69, 2%)	1,000
Type 2 Diabetes (n, %)	3 (30, 0%)	3 (23, 1%)	1,000

Dyslipidemia (n, %)	5 (50, 0%)	9 (69, 2%)	0,417
Atrial fibrillation (n, %)	2 (20, 0%)	2 (15, 4%)	1,000
Chronic kidney disease (n, %)	2 (20, 0%)	0 (0, 0%)	0,178
Psychiatric disease (n, %)	0 (0, 0%)	2 (15, 4%)	0,486
Active smoking (n, %)	2 (20, 0%)	4 (30, 8%)	0,660
Alcohol abuse (n, %)	0 (0, 0%)	2 (15, 4%)	0,486
Stroke aetiology			
Cardioembolic (n, %)	3 (30, 0%)	3 (23, 1%)	
Large vessel (n, %)	0 (0, 0%)	0 (0, 0%)	
Small vessel (n, %)	2 (20, 0%)	0 (0, 0%)	
Undetermined (n, %)	2 (20, 0%)	4 (30, 8%)	
Other (n, %)	0 (0, 0%)	2 (15, 4%)	
Haemorrhagic stroke (n, %)	3 (30%)	3 (23, 1%)	
Subaracnhoid haemorrhage (n, %)	0 (0, 0%)	1 (7, 7%)	

Table 1: Population with acute stroke divided according to the presence of persistent headache

Stroke aetiology was similar in both groups. Patients with other aetiologies were only noted on the "no persistent headache" group (spontaneous cervical dissection and venous infarct).

Most patients suffering from persistent headache used to suffer from previous chronic headache (Table 2). Of the 10 patients (43.5%) that had persistent headache, 8 clearly suffered from Previous Chronic Headaches (PCH), however, they all mentioned a different kind of persistent headache. Two patients had persistent headache despite not having PCH, but only 1 patient did other possible explanations for a secondary headache (1 patient had calcium channel blockers introduced during hospital stay). Thirteen patients (n=13/23, 56, 5%) were pain free at the follow-up and 4 patients which suffered from PCH, even ceased to have headache complaints.

Headache	With PCH	With no PCH
With no PHAPS	4	9
With PHAPS	8	2

Table 2: Relationship between previous chronic headache and persistent headache

There were considerable differences in the characteristics of previous, acute and persistent headaches (Table 5).

Headache type was more frequently migraine or tension type before stroke, but acute headache was mainly migraine type or with mixed characteristics. Persistent headache was more of the tension type or with mixed characteristics.

Pain localization was more frequently anterior and bilateral in all types of headache, but unilateral persistent headache was not typically ipsilateral to stroke, as opposed to acute headache. Pain was usually mild to moderate in most cases (n=7/10, 70, 0%). The majority (n=6/10, 60, 0%) had less than two episodes a month. Only 2 patients referred highly frequent episodes of 15 days a month.

Headache characterisation			
Type of headache (n, %)	**Previous**	**Acute**	**Persistent**
Migraine type	5 (50, 0%)	9 (39, 1%)	1 (10, 0%)
Tension type	4 (40, 0%)	2 (8, 7%)	5 (50, 0%)
Other	1 (10, 0%)	12 (52, 2%)	4 (40, 0%)
Headache localization (n, %)	Previous	Acute	Persistent
Anterior	7 (70, 0%)	18 (78, 3%)	6 (60, 0%)
Posterior	2 (20, 0%)	4 (17, 4%)	2 (20, 0%)
Hemicranial	0 (0, 0%)	0 (0, 0%)	2 (20, 0%)
Holocranial	0 (0, 0%)	1 (4, 3%)	0 (0, 0%)
Bilateral	7 (70, 0%)	16 (69, 6%)	5 (50, 0%)
Unilateral	2 (20, 0%)	6 (26, 1%)	4 (40, 0%)
Ipsilateral	-	6 (26, 1%)	2 (20, 0%)

Table 3: Persistent headache characterization, according to type and localization.

On the univariate logistic regression and multivariate logistic regression we observed a statistically significant association between the presence of previous chronic headache and persistent headache univariate analysis with an OR of 17,623 (1,287-244,374), p=0,027; multivariate analysis with an OR of 17,623 (1,287-244,374), p=0,032. The analysis also showed a trend towards a possible association between persistent headache and depressive symptoms univariate analysis with an OR 8,000 (0,725-88,226), p=0,090.

Size was not analysed because of the wide variability of stroke aetiologies, but NIHSS on admission may have served as a potential surrogate of this former factor.

Univariate logistic regression	OR	CI 95%	p value
Previous chronic headache history	9,000	1,285-63,025	0,027

Arterial territory	0,429	0,073-2,500	0,346
Cortical stroke	0,857	0,164-4,467	0,855
Hospital admission NIHSS	0,816	0,573-1,162	0,259
Calcium channel blockers at discharge	0,964	0,160-5,795	0,968
Epworth score at follow-up	0,930	0,718-1,206	0,586
PHQ-9 ≥ 8 questionnaire at follow-up	8,000	0,725-88,226	0,090

Table 4: Univariate logistic regression.

Multivariate logistic regression	OR	CI 95%	p value
Previous chronic headache	17,623	1,287-244,374	0,032
Hospital admission NIHSS	0,820	0,578-1,164	0,267
PHQ-9 questionnaire	1,457	0,089-23,877	0,792

Table 5: Forest plot for multivariate logistic regression.

Discussion

The main finding in our prospective cohort was that PCH was the only factor associated with persisting headache, perhaps only reflecting a change on the usual headache pattern. Interestingly, 4 patients which suffered from PCH, even ceased to have headache complaints. This hypothesis may be supported by the fact that persistent headache complaints were only ipsilateral to stroke in a minority of patients, as opposed to what is observed in the acute phase of stroke.

In this study only 1 patient seemed to have a persistent headache, corresponding to a very low percentage as compared to other studies in this area and similar to novel headache in reference subjects without stroke, serving as a control group. This is supported by the fact that headache prevalence seems to be similar in non-stroke populations [13,14]. As such, this study may question the existence of this new entity.

Little is known about the molecular and metabolic changes after stroke, but there is evidence for some network reorganization with recruitment of neighbouring and contralateral areas with similar functions as well as increased frontal lobe connectivity, possible reflecting executive back-up strategies for replacement of lost functions [15,16]. Recent studies showed a complex network on migraine pathophysiology with altered connectivity scattered through the brain (cortex, thalamus, hypothalamus, brainstem, amygdala and cerebellum) [17-24]. Likewise, in tension-type headache structural abnormalities have been shown along the pain matrix [25]. Disruption of the pain modulation network may explain the changes in headache patterns and, ultimately, explain total headache remission.

The population size didn't allow to draw back conclusions regarding a possible association between stroke aetiology and headache persistence as opposed to what has been extensively noted in acute phase headache [8; 26-40].

The strength of this study was clearly defining which patients already suffered from previous chronic headaches at patient admission, as this is a common complaint in the general population and was never assessed in previous similar studies. One of the biggest weaknesses was the stroke aetiology heterogeneity with the inclusion of mainly ischemic strokes, but also haemorrhagic strokes and subarachnoid haemorrhages, which may influence tissue reorganization in different ways.

Conclusion

In this study, only 10 out of 121 stroke patients (8.3%) mentioned persistent headache at the 6 to 12 month follow up, although the majority already suffered from PCH. Four patients were free of headache even though they used to suffer from PCH. We observed a change of the usual headache pattern.

Only 1 patient (<0, 1%) with persistent headache did not have a clear PCH history or association with other possible confounders. PCH history was the only clinical comorbidity associated with persistent headache. This study may question the existence of PHAPS.

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