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Weerd, N. van der; Pelzer, N.; Egberts, E.; Mertens, M.; Bakker, W.; Linstra, K.M.; ... ; Wermer, M.J.H.

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Changes in Migraine Symptoms after Ischemic Stroke: A Cohort Study

Nelleke van der Weerd[a, b] Nadine Pelzer[a] Emma Egberts[a] Marit Mertens[a] Willemijn Bakker[a] Katie M. Linstra[a] Arn M.J.M. van den Maagdenberg[a] Erik W. van Zwet[c] Antoinette MaassenVanDenBrink[d] Gisela M. Terwindt[a] Marieke J.H. Wermer[a, e]

[a]Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands; [b]Department of Human Genetics, Leiden University Medical Centre, Leiden, The Netherlands; [c]Department of Medical Statistics, Leiden University Medical Centre, Leiden, The Netherlands; [d]Department of Internal Medicine, Erasmus University Medical Centre, Rotterdam, The Netherlands; [e]Department of Neurology, Groningen University Medical Centre, Groningen, The Netherlands

Keywords
Migraine · Ischemic stroke · Comorbidity · Cerebral vasculature · Post-stroke

Abstract
Introduction: Migraine symptoms are postulated to improve post-stroke. We aimed to determine post-stroke changes in patients with active migraine pre-stroke and explored the relation with stroke location and stroke-preventive medication use. ***Methods:*** Patients with active migraine who had an ischemic stroke were retrieved from three research-cohorts between 2014 and 2021. By an interview, we retrospectively investigated first-year post-stroke changes for those ischemic stroke patients that suffered from migraine pre-stroke. Associations between change in migraine frequency/intensity/aura (decrease, no change, increase), stroke location (posterior location vs. other), and use of secondary stroke preventive medication were assessed by ordinal regression with adjustment for confounders. ***Results:*** We included 78 patients (mean age 48 years, 86% women, 47% with aura). Change in migraine symptomatology was reported by 63 (81%) patients; 51 (81%) noticed a decrease in attack frequency (27 no attacks) and 12 (19%) an increase. Pain intensity change was reported by 18 (35%) patients (50% increase, 50% decrease). Aura symptomatology improved in 4 (11%). Reduced attack frequency was not related to posterior stroke (OR = 1.5, 95% CI: 0.6–3.9), or preventive medication (antiplatelets OR = 1.0, 95% CI: 0.2–3.7; coumarin OR = 2.7, 95% CI: 0.4–20.6). ***Conclusions:*** Most patients with active pre-stroke migraine experience improvement of their symptoms in the first year after ischemic stroke. This change does not seem to be related to secondary stroke preventive medication or posterior stroke location.

Introduction

Migraine and ischemic stroke are closely connected. Migraine with aura is known to increase the risk of ischemic stroke approximately two-fold [1]. However, after ischemic stroke a reduction in migraine symptoms has

karger@karger.com
www.karger.com/ced

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Correspondence to:
Nelleke van der Weerd, n.van_der_weerd@lumc.nl

been reported in patients with cervical artery dissections (CADs) [2, 3]. There may be several reasons why migraine symptoms are affected by stroke. Disruption of the brainstem or occipital cortex due to stroke could hypothetically inhibit migraine (initiation). The brainstem has long been suggested to contain the migraine generator and is involved in important nociceptive pathways in migraine [4, 5]. Furthermore, the underlying mechanism of aura, cortical spreading depolarization, often originates in the occipital cortex [5]. Start of secondary preventive drugs after stroke might also influence migraine frequency and intensity [6, 7]. For example, clopidogrel and acetylsalicylic acid are reported to reduce migraine attack frequency, whereas dipyridamole might induce photophobia and headache in migraine patients [8]. Until now, only two small studies investigated the change of migraine symptoms after stroke. Both studies did not take the neuroanatomical connection between stroke and migraine into account. Therefore, we investigated migraine symptoms (attack frequency, pain intensity, migraine aura) a year pre- and post-stroke and explored whether possible changes in migraine symptoms post-stroke were related to posterior location of stroke or start of stroke preventive medication.

Methods

Ischemic stroke patients with a history of migraine (with and without aura) were selected from three research cohorts between February 2014 and August 2021: (1) Leiden University Medical Center Migraine Neuroanalysis program (LUMINA, with validated migraine e-questionnaire), a large study on migraine with and without aura (n = 2,400) [9], (2) Cardiovascular Risk profile in Women-Microvascular Status (CREW-MIST), a study on white matter lesions in women with ischemic stroke and migraine (n = 129), and (3) Dutch acute Stroke Trial (DUST), a large prospective national cohort study on ischemic stroke (n = 1,374) [10]. In the latter two cohorts, the Migraine Screener for Stroke (MISS) questionnaire was used [11] and migraine diagnosis was validated during a telephone interview, according to the International Classification of Headache Disorders (ICHD-3) [12]. Ischemic stroke was defined as acute neurological deficits lasting >24 h with a corresponding lesion seen on CT and/or MRI and classified into subtypes following TOAST classification [13]. When no clear classification was possible based on the medical files, we reported this as a missing. Stroke location was classified as posterior (brainstem, cerebellum, occipital lobes) or non-posterior (other locations).

A systematic interview was taken by telephone to, retrospectively, collect information on demographics, vascular risk factors, menopause, and medication use. Patients were asked to rate their migraine symptoms (frequency, pain intensity, aura) on four time points: year pre-stroke and 1, 6, and 12 months post-stroke. Patients without migraine attacks the year before stroke were excluded. Change in attack frequency was determined by the average of attacks the year before and after stroke. For patients from the CREW-MIST cohort, a shortened version of the interview was used, where symptoms were reported as decreased, unchanged, or increased. Determination of absolute change of attack frequency was not possible in this cohort. The study protocol was approved by the medical-ethical board of the LUMC (JGvD/jbt, approved on 29 October 2013).

Descriptive statistics were used for baseline characteristics and changes of migraine symptoms. To investigate differences between decrease/no change/increase of migraine symptoms, we used multivariable ordinal regression. Covariates were age, sex, location of stroke (posterior circulation yes/no), medication use (antiplatelets or coumarin derivates vs. none), start of menopause in the year after stroke (women only, yes/no). Odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Results

We included 78 patients (mean age at stroke onset 48 years, 86% women, 64% with aura, Table 1). The majority of ischemic strokes was caused by small vessel disease or of undetermined etiology. Six patients had other causes of ischemic stroke; none of them had CAD. Median time between stroke and the interview was 53 (IQR: 72) months.

In total, 63/78 (81%) patients noticed a change in migraine symptoms in the first year, of which 81% reported a decrease (43% symptom free) and 19% an increase (Fig. 1). Patients reported a median decrease in frequency of 50% (IQR: 80) and a median increase of 164% (IQR: 483). Change of pain intensity was reported by 35% patients and was equally divided into worsening and improvement. Of the 37 migraine with aura patients, 11% reported decreased aura symptoms and 81% noticed no change in aura symptoms (8% patients did not answer). Migraine prophylactic medication use was decreased in 2/63 and increased in 1/63 patient. No clear differences between migraine with or without aura were found for any of the changes in migraine symptoms. For detailed information on the changes in migraine symptoms, see online supplementary file (for all online suppl. material, see https://doi.org/10.1159/000539421). Posterior location (OR = 1.5, 95% CI: 0.6–3.9), medication use (antiplatelets OR = 1.0, 95% CI: 0.2–3.7; coumarin derivatives OR = 2.7, 95% CI: 0.4–20.6), and menopause (OR = 1.1, 95% CI: 0.4–3.4) were not associated with reduced migraine attack frequency after stroke (Table 2).

Discussion

Our study shows that changes in migraine symptoms occur in the majority of patients after ischemic stroke. In most patients, attack frequency improved, with cessation

Table 1. Baseline characteristics

	Total (*n* = 78)	Migraine without aura (*n* = 28)	Migraine with aura (*n* = 50)
Women, *n* (%)	67 (86)	26 (93)	41 (82)
Age at stroke, years±SD	48±10	45±8	50±11
Follow-up, median (IQR), months	53 (72)	69 (69)	48 (67)
Migraine frequency per year, median (IQR)	12 (18)	12 (18)	12 (19)
Vascular risk factors, *n* (%)			
Hypertension	39 (50)	15 (54)	24 (48)
Hypercholesterolemia	35 (45)	17 (61)	18 (36)
Diabetes mellitus	7 (9)	1 (4)	6 (12)
TIA	6 (8)	1 (4)	5 (10)
Ever smoked	50 (64)	20 (71)	30 (60)
Smoking pack, years±SD	16±13	12±11	19±14
Alcohol (>2 units/day)	1 (1)	0 (0)	1 (2)
TOAST classification, *n* (%)			
LAA	10 (13)	4 (14)	6 (12)
CE	5 (6)	2 (7)	3 (6)
SVD	17 (22)	8 (29)	9 (18)
Undetermined	31 (40)	12 (43)	19 (38)
Other cause	6 (8)	0 (0)	6 (12)
Missing	9 (11)	2 (7)	7 (14)

TIA, transient ischemic attack; LAA, large artery atherosclerosis; CE, cardiac emboli; SVD, small vessel disease.

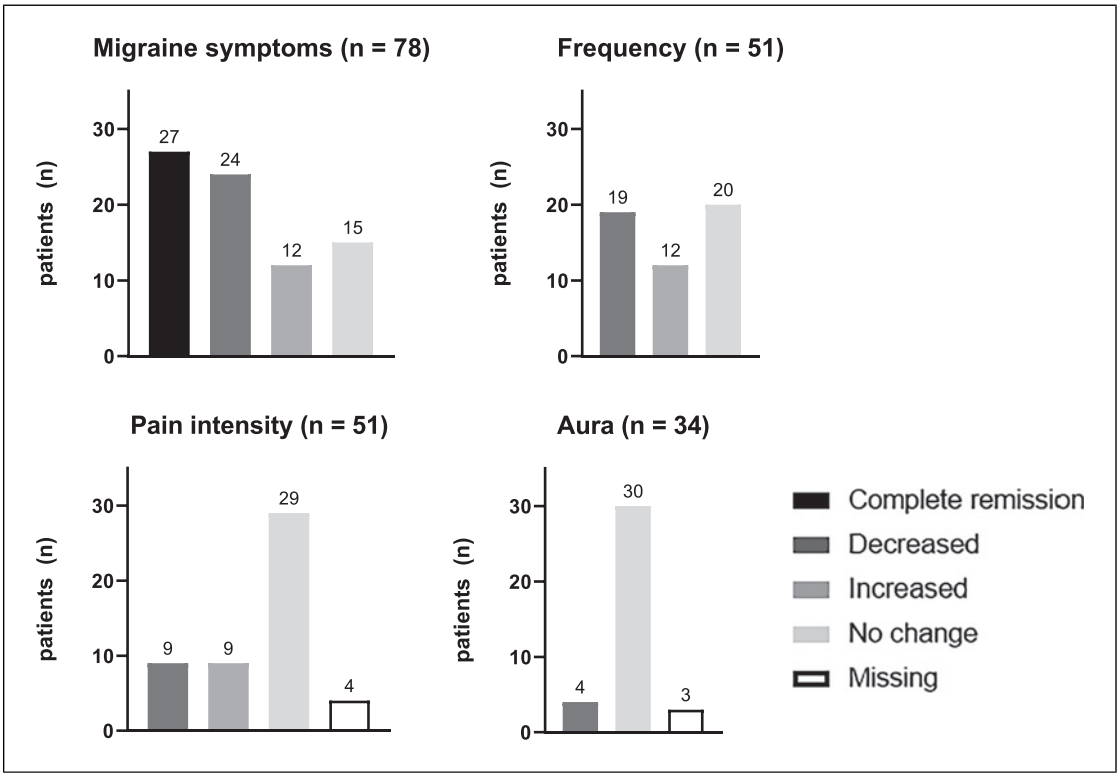

Fig. 1. Flowchart showing migraine symptoms after stroke.

Table 2. Patient characteristics after stroke

	All (n = 78)	Decreased (n = 51)	No change (n = 15)	Increased (n = 12)
Women, n (%)	57 (73)	43 (84)	14 (93)	10 (83)
Quit smoking after stroke, n (%)	14 (18)	11 (22)	1 (7)	1 (8)
Start of menopause after stroke, n (%)	21 (27)	15 (29)	3 (20)	3 (25)
Stroke medication, n (%)				
Antiplatelets	59 (76)	40 (78)	11 (73)	8 (67)
Coumarin derivatives	7 (9)	3 (6)	3 (20)	1 (8)
Stroke location, n (%)				
Left hemisphere	22 (28)	13 (25)	6 (40)	3 (25)
Right hemisphere	23 (29)	17 (33)	2 (13)	4 (33)
Occipital	10 (13)	6 (12)	3 (20)	1 (8)
Cerebellar	7 (9)	3 (6)	1 (7)	3 (25)
Brainstem	11 (14)	9 (18)	2 (13)	0 (0)
Non-posterior	5 (6)	2 (4)	1 (7)	2 (17)

of attacks reported by one-third of patients. Pain intensity changed in a third but can either be increased or decreased, and aura remained relatively unchanged. We found no association with stroke location or use of stroke preventive medication. Almost half of our patients had migraine with aura. This proportion might seem disproportionate to the general population of migraine patients in which one-third has aura symptoms. However, in our opinion this is not very surprising as migraine with aura is in particular a risk factor for ischemic stroke.

Two previous studies investigating migraine symptoms after stroke found comparable results albeit they focused on patients with CAD [2, 3]. The first (n = 43) reported improvement of attack frequency in 80% of CAD patients (50% symptom free) [3]. The second (n = 87) found decreased migraine frequency in 60% of the patients (15% symptom free). This study also included a small number of non-CAD patients in whom 44% reported relief of migraine [2]. In contrast to these previous studies, in our study none of the patients was known with CAD. However, we cannot rule out that some of our patients had ischemic stroke caused by CAD as in 11% of our patients the cause of stroke was missing. Both studies did not investigate the effect of stroke location and common medication use.

Several explanations for the stroke-migraine relation include CAD, endothelial dysfunction, and hypercoagulability. The latter results in emboli, which can cause CSD and migraine aura [14]. Possibly, there are fewer emboli post-stroke, leading to improvement of migraine after stroke.

Although 27% of the patients went through menopause around the same time stroke occurred, we found no association of changes in migraine and menopause. However, we did not include a control group and, therefore, we could not perform an in-depth analysis of the effect of stroke on the natural course of migraine independently of perimenopause. Moreover, we found no clear association between antiplatelet use and changes in migraine symptoms. This is in line with previous research that showed that patients with decrease in migraine symptoms were similar to a placebo group with regard to use of antiplatelets [15]. However, our results should be interpreted with caution because of the limited sample size as the results from larger trials point toward a moderate prophylactic effect of acetylsalicylic acid for the prophylaxis of migraine, especially in patients with migraine with aura [16]. Furthermore, we found 9/11 patients with brainstem stroke reported less migraine attacks, but we could not show a significant difference. Both are likely due to our limited sample size. Interestingly, headache occurs more after posterior stroke [17]. Unfortunately, we have no detailed information on the exact stroke location on MRI because we did not have access to the original images. Therefore, we could not investigate whether a cortical or subcortical lesion was associated with improvement of migraine symptoms after stroke. Other limitations are the retrospective design with self-reported symptoms, inevitably inducing recall bias, and the lack of a control group [18, 19]. However, we consider complete remission of migraine symptoms a major change for patients, and, therefore, believe complete remission is an event remembered well by patients. Thus, recall bias might have less impact on our finding of complete remission, compared with findings of reduced/increased migraine

symptoms [15]. Strengths are inclusion of patients with all stroke subtypes increasing generalizability.

We conclude that migraine symptoms may change in the first year post-stroke for those with active migraine prior to the stroke, with mostly an improvement of attacks. This knowledge could be used to inform migraine patients, who suffered from stroke, about the prognosis of their migraine symptoms. Future larger studies are needed to clearly identify underlying mechanisms and to confirm whether location of stroke is associated with improvement of migraine symptom. This could further increase our insight in the migraine-stroke association.

Statement of Ethics

This study protocol was reviewed and approved by the medical-ethical board of the Leiden University Medical Centre, approval number JGvD/jbt. Written informed consent was obtained from participants to participate in the study.

Conflict of Interest Statement

G.M.T. reports consultancy or industry support from AbbVie/Allergan, Lilly, Lundbeck, Novartis, Pfizer, and Teva and independent support from the European Community, Dutch Heart and Brain Foundations, Dutch Research Council, IRRF, and Diaraphte. A.M.V.D.B. received honoraria and research and/or travel grants from Allergan/AbbVie, Amgen/Novartis, Eli Lilly, Pfizer, Satsuma, Teva, and Tonix as principal investigator and independent support from the Dutch Research Council and ZonMw.

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Author Contributions

N.P., G.T., A.M.V.D.B., and M.W. contributed substantially to the conception and design of the study. N.P. advised on interpretation of data and substantially contributed to the writing of the manuscript. E.Z. advised on the statistical analysis. N.P., N.W., E.E., K.L., M.M., and W.B. contributed substantially to collecting and interpretation of data. N.W. did the principal data analysis and writing of the manuscript. N.P., M.W., G.T., A.M.V.D.B., K.L., A.M.J.M., and E.Z. contributed to revising the article, and all authors approved the final version as submitted.

Data Availability Statement

The data are not publicly available as they contain sensitive information from patients. Further inquiries can be directed to the corresponding author.

References

1 Adelborg K, Szépligeti SK, Holland-Bill L, Ehrenstein V, Horváth-Puhó E, Henderson VW, et al. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. BMJ. 2018;360:k96. https://doi.org/10.1136/bmj.k96

2 Censori B, Partziguian T, Poloni M. Migraine improves after ischemic stroke. J Stroke Cerebrovasc Dis. 2013;22(8):e338–42. https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.02.014

3 De Giuli V, Graziano F, Zini A, Zedde M, Patella R, Lodigiani C, et al. Migraine improvement after spontaneous cervical artery dissection the Italian Project on Stroke in Young Adults (IPSYS). Neurol Sci. 2019;40(1):59–66. https://doi.org/10.1007/s10072-018-3578-9

4 Borsook D, Burstein R. The enigma of the dorsolateral pons as a migraine generator. Cephalalgia. 2012;32(11):803–12. https://doi.org/10.1177/0333102412453952

5 Ferrari MD, Klever RR, Terwindt GM, Ayata C, van den Maagdenberg AMJM. Migraine pathophysiology: lessons from mouse models and human genetics. Lancet Neurol. 2015;14(1):65–80. https://doi.org/10.1016/S1474-4422(14)70220-0

6 Le H, Tfelt-Hansen P, Skytthe A, Kyvik KO, Olesen J. Association between migraine, lifestyle and socioeconomic factors: a population-based cross-sectional study. J Headache Pain. 2011;12(2):157–72. https://doi.org/10.1007/s10194-011-0321-9

7 Sacco S, Ricci S, Degan D, Carolei A. Migraine in women: the role of hormones and their impact on vascular diseases. J Headache Pain. 2012;13(3):177–89. https://doi.org/10.1007/s10194-012-0424-y

8 Hawkes CH. Dipyridamole in migraine. Lancet. 1978;2(8081):153. https://doi.org/10.1016/s0140-6736(78)91534-9

9 van Oosterhout WP, Weller CM, Stam AH, Bakels F, Stijnen T, Ferrari MD, et al. Validation of the web-based LUMINA questionnaire for recruiting large cohorts of migraineurs. Cephalalgia. 2011;31(13):1359–67. https://doi.org/10.1177/0333102411418846

10 van Seeters T, Biessels GJ, Kappelle LJ, van der Schaaf IC, Dankbaar JW, Horsch AD, et al. The prognostic value of CT angiography and CT perfusion in acute ischemic stroke. Cerebrovasc Dis. 2015;40(5–6):258–69. https://doi.org/10.1159/000441088

11 van der Willik D, Pelzer N, Algra A, Terwindt GM, Wermer MJH. Assessment of migraine history in patients with a transient ischemic attack or stroke; validation of a migraine screener for stroke. Eur Neurol. 2017;77(1–2):16–22. https://doi.org/10.1159/000449425

12 Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders Disorders, 3rd editio. Cephalalgia. 2018;38(1):1–211.

13 Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35–41. https://doi.org/10.1161/01.str.24.1.35

14 Tietjen GE, Maly EF. Migraine and ischemic stroke in women. A narrative review. Headache: J Head Face Pain. 2020;60(5):843–63. https://doi.org/10.1111/head.13796

15 Diener HC, Hartung E, Chrubasik J, Evers S, Schoenen J, Eikermann A, et al. A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. Cephalalgia. 2001;21(2):120–8. https://doi.org/10.1046/j.1468-2982.2001.00168.x
16 Diener HC. Editorial commentary. Cephalalgia. 2001;21(3):167–8. https://doi.org/10.1046/j.0333-1024.2001.00204.x
17 Harriott AM, Karakaya F, Ayata C. Headache after ischemic stroke: a systematic review and meta-analysis. Neurology. 2020;94(1):e75–86. https://doi.org/10.1212/WNL.0000000000008591
18 Miller VE, Faurot KR, Palssson OS, MacIntosh BA, Suchindran C, Honvoh G, et al. Comparing prospective headache diary and retrospective four-week headache questionnaire over 20 weeks: secondary data analysis from a randomized controlled trial. Cephalalgia. 2020;40(13):1523–31. https://doi.org/10.1177/0333102420949180
19 van Casteren DS, Verhagen IE, de Boer I, de Vries Lentsch S, Fronczek R, van Zwet EW, et al. E-diary use in clinical headache practice: a prospective observational study. Cephalalgia. 2021;41(11–12):1161–71. https://doi.org/10.1177/03331024211010306