Received: 1 July 2023 | Accepted: 22 January 2024

DOI: 10.1111/head.14682

RESEARCH SUBMISSIONS

Characteristics of acute ischemic stroke and unusual aura in patients with migraine with aura

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Funding information
Swiss Heart Foundation, Grant/Award Number: FF21070

Abstract

Background: Sometimes migraine aura changes from attack to attack, raising the question of whether the change is heralding an ischemic stroke or an unusual aura. Differentiating unusual migraine aura from the onset of an acute ischemic stroke in patients with migraine with aura (MwA) can be challenging.

Objective: The aim of this cohort study was to assess clinical characteristics that help distinguish between MwA and minor stroke in patients with a previous history of MwA who presented with suspicion of stroke.

Methods: We interviewed patients with MwA and ischemic stroke (MwA + IS) and patients with MwA and unusual aura, but without ischemic stroke (MwA − IS) from a tertiary hospital using a structured questionnaire. We assessed how symptoms of ischemic stroke or unusual aura differed from usual, that is, the typical aura in each patient. Stroke or exclusion of stroke was verified by multimodal magnetic resonance imaging.

Results: Seventeen patients with MwA + IS and twelve patients with MwA − IS were included. New focal neurological symptoms (13/17 [76%] vs. 3/12 [25%]), change of the first symptom (10/17 [59%] vs. 1/12 [8%]), and absence of headache (6/15 [40%] vs. 2/10 [20%]) were more often reported during ischemic stroke. The physical examination was normal in 8/17 (47%) MwA + IS and in 6/12 (50%) MwA − IS patients. In 5/17 (29%) patients with MwA + IS, there were unequivocal physical signs suggestive of stroke such as persistent visual loss, ataxia, or paresis.

Conclusion: There are clues from the history that might help identify stroke in patients with MwA with changed aura symptoms. These might be particularly useful in patients presenting without physical findings suggestive of stroke.

Plain Language Summary: Sometimes migraine aura symptoms change from attack to attack, raising the question of whether the change is heralding an ischemic stroke or simply an unusual aura. In patients with migraine with aura, we compared symptoms of

Abbreviations: CI, confidence interval; CSD, cortical spreading depression; ICHD-3, International Classification of Headache Disorders, 3rd edition; IQR, interquartile range; IS, ischemic stroke; MRI, magnetic resonance imaging; MwA, migraine with aura; NIHSS, National Institutes of Health Stroke Scale; PFO, patent foramen ovale; SD, standard deviation.

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unusual aura in patients who had ischemic stroke on imaging versus those who did not. Patients who had ischemic stroke were more likely to report new neurological symptoms (such as visual, sensory, speech, or motor symptoms), change of first occurring symptom (e.g., sensory instead of the usual visual), and absence of headache during the attack.

KEYWORDS
ischemic stroke, non-stereotyped migraine aura, stereotyped migraine aura

INTRODUCTION

Migraine with aura (MwA) in its acute stage includes acute ischemic stroke as an important differential diagnosis. In clinical practice, a change of aura type in patients with MwA might be caused by an incident ischemic stroke or an unusual migraine aura. This differentiation can pose problems because patients with ischemic stroke sometimes report migraine-like symptoms.[1] Furthermore, the ischemic stroke in patients with known MwA might manifest by a change of migraine aura phenotype.[2] Complicating the matter even further, patients with MwA might experience a change of migraine aura symptoms from aura to aura, without suffering a stroke.[3] There is a paucity of data on the clinical characteristics of stroke in patients with MwA.[2,4,5]

We aimed to identify clinical characteristics that help distinguish between MwA and minor stroke in patients with a previous history of MwA who present with suspicion of stroke. We hypothesized that there are symptoms and physical findings that might help to discriminate on a clinical basis between stroke and unusual migraine aura.

METHODS

This is a descriptive cohort study. Using a structured questionnaire (Supplemental File), we interviewed patients with MwA and ischemic stroke (MwA+IS) as well as patients with MwA without stroke (MwA−IS). We focused on the symptoms of usual aura and ischemic stroke in the MwA+IS group and of usual and unusual aura in the MwA−IS group.

Inclusion and exclusion criteria

For the MwA+IS group, patients from a previous study[1,6] were identified and included based on the following inclusion criteria: (a) a diagnosis of ischemic stroke proven by multimodal magnetic resonance imaging (MRI) according to the American Heart Association/American Stroke Association (AHA/ASA) definition,[7] (b) known diagnosis of MwA according to the International Classification of Headache Disorders, 3rd edition (ICHD-3),[8] (c) the last usual migraine aura attack occurred within 12 months prior to the interview, and (d) the ischemic stroke occurred within 6 months prior to the interview. For the MwA+IS group, a secondary analysis of previously collected data was performed.[1,6] No screening for MwA was conducted and only patients with a known history of MwA were included. The patients were treated at our tertiary hospital in our stroke center or outpatient headache clinic between June 2019 and February 2022.

For the MwA−IS group, we identified additional consecutive patients between March and October 2022 presenting at our emergency department for suspicion of ischemic stroke with the following inclusion criteria: (a) known diagnosis of MwA according to the ICHD-3, (b) the last usual migraine aura attack occurred within 12 months prior to the interview, (c) the unusual migraine aura differed from the usual migraine aura with regard to at least one characteristic of the ICHD-3 C-criterion, and (d) absence of ischemic injury on acute MRI and no suspicion of a vascular event as an explanation for the unusual migraine aura. For the MwA−IS group, we included only patients with acute MRI imaging due to the low sensitivity of computed tomography scans to detect brain ischemia.[9]

Exclusion criteria for both groups were age <18 years and cognitive deficits precluding a useful interview.

We did not conduct additional interviews with the same participants to calculate interrater variability and the consistency of the participant's responses, as this might lead to diagnostic variability.[10]

The diagnosis of previous MwA was made by board-certified neurologists and verified using the questionnaire by the lead and senior authors (A.S. and C.J.S., respectively).

Further definitions

Diabetes mellitus was defined as HbA1c>6.5%, arterial hypertension as antihypertensive treatment or blood pressure of 140/90 mmHg or higher, and dyslipidemia when low-density lipoprotein exceeded 2.6 mmol/L or when lipid-lowering treatment was given. In the case of patent foramen ovale (PFO)–associated stroke, the PFO-Associated Stroke Causal Likelihood (PASCAL) classification was used to assess the causality between PFO and stroke.[11]

Statistical analysis

For the statistical analysis, STATA MP 16.0 (StataCorp LCC) was used. The frequencies of binomial variables are presented as counts. The continuous variables are presented as means and standard deviations or medians and 25%–75% interquartile ranges (IQR), as appropriate. We calculated 95% confidence intervals (CI) for proportions using the Wilson method. We looked at the differences between the usual aura and the ischemic stroke in MwA+IS group and between the usual and the unusual aura in the MwA−IS group. Specifically, we analyzed the occurrence of new symptoms, absence of known symptoms, change of first occurring symptom (e.g., sensory instead of visual), change of symptom type of at least one symptom, change of symptom onset time

of at least one symptom, change of symptom duration of at least one symptom, change of headache characteristics, and change of temporal succession of headache and aura. Furthermore, we assessed the frequency of absence of physical signs in the acute phase of stroke and unusual MwA. In addition, we looked at changes in C-characteristics of ICHD-3 criteria for migraine aura between usual aura and stroke in the MwA+IS group and between usual aura and unusual aura in the MwA−IS group. Given the exploratory nature of this study, no prior sample-size calculation has been performed. The sample size was based on the available data. There were no missing data.

Ethics

The study has been approved by the ethics committee of canton Bern (KEK 2018-02258). Written informed consent was obtained from all participants prior to the interview.

TABLE 1 Distribution of the vascular risk factors in patients with migraine aura with and without ischemic stroke.

Vascular risk factors	MwA+IS[a] (*N* = 17)	MwA−IS[a] (*N* = 12)
Active smoking, *n* (%)	6 (35)	3 (25)
Chronic alcohol abuse, *n* (%)	0	1 (8)
Recreational drugs, *n* (%)	0	0
High blood pressure, *n* (%)	6 (35)	1 (8)
Diabetes mellitus, *n* (%)	0	0
Dyslipidemia, *n* (%)	10 (59)	0
Depression, *n* (%)	3 (18)	2 (17)
Atrial fibrillation, *n* (%)	0	0
Chronic inflammatory disease, *n* (%)	0	2 (17)[b]

[a]MwA+IS: migraine aura with ischemic stroke; MwA−IS: migraine aura without ischemic stroke.

[b]One patient with Chron's disease and pulmonary sarcoidosis, one patient with giant cell arteritis.

RESULTS

After the exclusion of three patients with the last usual aura >1 year prior, seventeen were included in the MwA+IS group. After screening 31 potentially eligible patients, 12 patients were included in the MwA−IS group. Reasons for exclusion were: last usual aura was >1 year prior to the interview ($n = 2$), refusal of participation ($n = 5$), could not be reached ($n = 6$), and no change of usual aura ($n = 6$).

There were 9/17 (52%) women in the MwA+IS and 8/12 (66%) in the MwA−IS group. The mean age was 55 years (SD ±16) and 51 years (SD ±16) in the MwA+IS and MwA−IS groups, respectively. Patients in the MwA+IS group were interviewed after a median of 18 days (IQR 6–131) after the last usual migraine aura and 2 days (IQR 1–8) after the ischemic stroke. Patients in the MwA−IS group were interviewed after a median of 80 days (IQR 28–150) after the last usual migraine aura and 14 days (IQR 6.5–30) after the unusual aura. In the MwA+IS group, the median National Institutes of Health Stroke Scale (NIHSS) was 0 (IQR 0–1), and in the MwA−IS group, the median NIHSS was 0 (IQR 0–1) as well. The distribution of the vascular risk factors is given in Table 1.

In 13/17 (76%, 95% CI 53–90) of the MwA+IS and 10/12 (83%, 55–95) of the MwA−IS groups, the C-criterion of the ICHD-3 was fulfilled (Table 2).

In the MwA+IS and MwA−IS groups, respectively, new neurological symptoms were reported by 13/17 (76%, 95% CI 52–90) and 3/12 (25%, 95% CI 9–53) patients. The absence of known neurological symptoms was described by 9/17 (53%, 95% CI 31–74) and 2/12 (17%, 95% CI 5–45) respectively. The first occurring symptom changed in 10/17 (59%, 95% CI 36–68) of the MwA+IS and 1/12 (8%, 95% CI 1–35) of the MwA−IS patients. In the MwA+IS group, the change of first symptom was reported as follows: eight had sensory instead of visual symptoms, one had vertigo instead of visual symptoms, and one had paresis instead of visual symptoms. In one patient, the symptoms during the stroke closely resembled the usual

TABLE 2 The C-criterion for migraine aura according to the International Classification of Headache Disorders, 3rd edition during the ischemic stroke and unusual aura in patients with migraine with aura.

	MwA+IS[a] (*N* = 17)	Changes of C-criteria in MwA+IS[c]	MwA−IS[a] (*N* = 12)	Changes of C-criteria in MwA−IS[d]
C1: At least one aura symptom spreads gradually over ≥5 min, *n* (%)	7 (41)	7 (41)	7 (58)	3 (25)
C2: Two or more aura symptoms occur in succession, *n* (%)	6 (35)	6 (35)	7 (58)	3 (25)
C3: Each individual aura symptom lasts 5–60 min, *n* (%)	3 (18)	13 (76)	6 (50)	5 (42)
C4: At least one aura symptom is unilateral, *n* (%)	17 (100)	3 (18)	8 (67)	2 (17)
C5: At least one aura symptom is positive, *n* (%)	12 (71)	7 (41)	7 (58)	3 (25)
C6: The aura is accompanied, or followed within 60 min, by headache, *n* (%)	10 (59)[b]	9 (53)	8 (67)[b]	2 (17)
C-criterion fulfilled (= at least three fulfilled characteristics), *n* (%)	13 (76)	4 (24)	10 (83)	2 (17)

[a]MwA+IS: migraine aura with ischemic stroke; MwA−IS: migraine aura without ischemic stroke.

[b]Only in patients with headache during the habitual aura.

[c]Changes of C-criteria during the stroke compared to the usual aura.

[d]Changes of C-criteria during the unusual aura compared to the usual aura.

TABLE 3 Change of headache characteristics during the ischemic stroke and unusual aura.

	MwA + IS[a] (*N* = 7)	MwA − IS[a] (*N* = 8)
Change of headache location, *n* (%)	3 (43)	5 (63)
Change of headache character, *n* (%)	3 (43)	2 (25)
Change of headache intensity,[b] *n* (%)	2 (29)	5 (63)
Change of aggravation upon movement, *n* (%)	2 (29)	0
Change of photophobia, *n* (%)	1 (14)	3 (38)
Change of phonophobia, *n* (%)	1 (14)	1 (13)
Change of nausea, *n* (%)	4 (57)	2 (25)

[a]MwA + IS: migraine aura with ischemic stroke; MwA − IS: migraine aura without ischemic stroke.

[b]Change of at least two points on numeric rating scale.

aura (visual disturbance with scintillating scotoma) but had a longer duration.

A change of symptom type of at least one symptom (e.g., positive to negative or vice versa) was described by 7/17 (41%, 95% CI 22–64) MwA + IS and 4/12 (33%, 95% CI 14–61) MwA - IS patients, respectively. A change of onset time of at least one symptom was reported by 6/17 (35%, 95% CI 17–59) and 6/12 (50%, 25–75) patients. Changes of the C-criteria during the stroke and unusual aura compared to the usual aura are given in Table 2. During the stroke, the C3-criterion (each individual aura symptom lasts 5–60 min) changed most frequently (13/17, 76% [95% CI 53–90]).

Fifteen and ten patients in the MwA + IS and MwA − IS groups, respectively, had headache during the usual aura. The headache characteristics changed in 7/15 (47%, 95% CI 25–70) and 8/10 (80%, 49–94) of MwA + IS and MwA − IS groups, respectively (Table 3). The headache was absent in 6/15 (40%, 95% CI 20–64) during the stroke and in 2/10 (20%, 95% CI 6–51) during the unusual aura. Four of 15 (27%, 95% CI 11–52) reported a change of succession between headache and focal neurological symptoms during the stroke, while no patient in the MwA − IS group reported such a change.

In each group, one patient had an aura status defined according to the current criteria[8] (6%, 95% CI 1–27 vs. 8%, 95% CI 1–35).

Eight of 17 patients (47%, 95% CI 26–69) in the MwA + IS group, and 6/12 patients (50%, 95% CI 25–75) in the MwA − IS group showed physical signs suggestive of ischemic stroke. Persistent visual loss, ataxia, or paresis as physical signs were present only in the MwA + IS group (5/17, 29%, 95% CI 13–53). Physical findings of both groups and stroke characteristics of the MwA + IS group are given in Table 4. Detailed characteristics of MwA + IS and MwA − IS groups are given in Supplemental Tables in supporting information.

TABLE 4 Characteristics of ischemic stroke and unusual aura in migraine with aura patients.

	MwA + IS[a] (*N* = 17)	MwA − IS[a] (*N* = 12)
Physical signs		
None, *n* (%)	9 (53)	6 (50)
Persistent sensory disturbance, *n* (%)	3 (18)	4 (33)
Persistent speech disturbance, *n* (%)	0	2 (17)
Other,[b] *n* (%)	5 (29)	0
Wake-up (MwA + IS only), *n* (%)	3 (18)	n/a
Stroke etiology (MwA + IS only), *n* (%)		n/a
PFO-associated stroke, *n* (%)	7 (41)	n/a
Acc. to PASCAL[c] possible causal relatedness, *n* (%)	3 (18)	n/a
Acc. to PASCAL[c] probable causal relatedness, *n* (%)	4 (24)	n/a
Large artery atherosclerosis, *n* (%)	2 (12)	n/a
Small vessel occlusion, *n* (%)	1 (6)	n/a
Stroke of undetermined etiology, *n* (%)	7 (41)	n/a
Stroke location (MwA + IS only)[d]		
MCA, *n* (%)	5 (29)	n/a
PCA (including diencephalon), *n* (%)	6 (35)	n/a
Vertebrobasilar, *n* (%)	2 (12)	n/a
Multiple territories,[e] *n* (%)	4 (24)	n/a

Abbreviation: PFO, patent foramen ovale.

[a]MwA + IS: migraine aura with ischemic stroke; MwA − IS: migraine aura without ischemic stroke.

[b]Persistent visual deficit *n* = 1, persistent visual, sensory and motor deficit *n* = 2, persistent speech and motor deficit *n* = 1, persistent ataxia *n* = 1.

[c]PASCAL, PFO-Associated Stroke Causal Likelihood.

[d]MCA, middle cerebral artery; PCA, posterior cerebral artery.

[e]Scattered ischemic lesions in the left watershed region MCA/PCA, left watershed region MCA/ACA, and in the left PCA territory *n* = 1, bilateral occipital lobes and cerebellar, PCA and SCA territories *n* = 1, left thalamic, left occipital lobe, left cerebellar hemisphere in PCA territory *n* = 1, right centrum semiovale (MCA territory), cerebellar left (superior cerebellar artery territory).

DISCUSSION

The main findings of our study to compare ischemic stroke and unusual migraine aura in patients with MwA with and without stroke are: (1) a higher proportion of patients with stroke reported new neurological symptoms, lack of known neurological symptoms, change of first symptom, and lack of headache; (2) the C-criterion of the ICHD-3 was fulfilled in similar proportions during the ischemic stroke and the unusual migraine aura; and (3) in one third of patients with stroke, there were unequivocal physical signs suggestive of stroke such as persistent visual loss, ataxia, or paresis, but the neurological examination was normal in half of stroke patients.

It is well known that almost all patients with MwA experience visual symptoms, suggesting that the cortical spreading depression (CSD), the pathophysiological basis of migraine aura, predominantly affects the occipital lobe.[10,12] During ischemic stroke, emboli may affect other parts of the brain, explaining the different distribution of symptoms in stroke and MwA.[13] Therefore, it is plausible that the occurrence of new symptoms, lack of known symptoms, and a

change of first occurring symptom are reported more frequently by patients with MwA during ischemic stroke compared to unusual migraine aura. In our series, all patients with a change of first symptom during the stroke had, in their usual aura, visual symptoms as the first occurring symptom.

In our series, the lack of headache was reported by a higher proportion of patients with stroke. The presence of headache at the onset of ischemic stroke might be influenced by stroke characteristics such as location in the vertebrobasilar territory or cardioembolic etiology.[14] Limited by the very low sample size, we could not perform adjusted analyses to correct for such factors, and future adequately powered studies are needed.

Surprisingly, the ICHD-3 C-criterion was fulfilled in similar proportions during the ischemic stroke and the unusual aura. This suggests that migraine-like symptoms defined according to ICHD-3 criteria may not be specific for migraine aura in patients with known MwA.[2,4] Therefore, a fulfilled C-criterion should not negate the suspicion of stroke in patients with MwA with changed aura symptoms. Patients with MwA might have a lower threshold for CSD in response to various stimuli, including ischemic injury. Ischemia-induced CSD might cause positive and slowly occurring symptoms, thus mimicking symptoms of aura during the ischemic stroke.[2,6] Previously, we found that comorbid MwA was associated with a higher rate of migraine aura-like symptoms at the onset of ischemic stroke (unadjusted odds ratio 8.66, 2.44–46.64).[6]

Looking at changes in the individual C-criteria, the C3-criterion changed most often. This was due mostly to persistent symptoms, rather than symptoms of very short duration of <5 min (Supplemental Tables). Adequately powered prospective studies are needed to assess which changes in C-characteristics are most helpful in differentiating stroke from an unusual migraine aura. This is especially important because even in the absence of stroke, prolonged aura symptoms are not uncommon.[15]

Given that an aura status was seen in one MwA + IS patient, its occurrence may herald acute ischemic stroke, in line with previous reports.[2,16,17]

Last, the proportions of patients with and without physical findings in the acute phase were similar. This is of particular clinical importance, because in half of patients with MwA with ischemic stroke, clues suggestive of stroke could be derived from the history of symptoms only.[13] That being said, in one third of patients with stroke (29%), certain physical findings, such as motor disturbance or ataxia, unequivocally suggested ischemic stroke.

The main limitation of our study is the low number of included patients, precluding us from drawing firm conclusions. Therefore, the results should be seen as hypothesis-generating only and could be used to design adequately powered studies to further investigate this topic. Even so, its strength lies in the rigorous clinical phenotyping with a gold standard evaluation of stroke diagnosis using acute neuroimaging in both groups. Further limitations include the duration between the last usual migraine aura and the interview in both groups, which was 18 and 80 days with large interquartile ranges, making the results susceptible to a recall bias. Because the patients had usual aura multiple times during their lifetime, the effect of recall bias is probably reduced. Still, we cannot exclude a recall bias in the MwA – IS group, because the median number of days between unusual aura and interview was 14 days (IQR 6.5–30). A late onset (>50 years) of migraine aura-like events should be regarded as a red flag for underlying brain pathology; however, we did not assess the age of the first occurrence of MwA. Furthermore, we cannot exclude a transient ischemic attack or MR-negative ischemic minor stroke as a cause for the unusual aura symptoms in the MwA – IS group. Last, we defined an unusual migraine aura as a changed aura with regard to at least one characteristic of the ICHD-3 C-criterion to avoid the impression that minor changes in aura characteristics should cause concern for stroke. Besides the type of symptoms as positive versus negative, we did not analyze changes in the characteristics of the visual or sensory disturbance, given their heterogeneity[3,13] and the low number of patients included. Therefore, larger studies are needed to identify changes in characteristics of visual and/or sensory symptoms that may be regarded as red flags.

In conclusion, a higher proportion of patients with stroke reported new neurological symptoms, lack of known neurological symptoms, change of first symptom, and lack of headache. In one third of patients with stroke, there were unequivocal physical signs suggestive of stroke such as persistent visual loss, ataxia, or paresis, but in half of stroke patients, the neurological examination was normal. The symptoms of ischemic stroke and those of unusual aura fulfilled the ICHD-3 C criterion in similar proportions.

AUTHOR CONTRIBUTIONS

Adrian Scutelnic: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; supervision; writing – original draft; writing – review and editing. **Nathalie L. Sutter:** Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Morin Beyeler:** Data curation; investigation; writing – review and editing. **Thomas R. Meinel:** Formal analysis; methodology; writing – review and editing. **Franz Riederer:** Formal analysis; writing – review and editing; writing – review and editing. **Urs Fischer:** Validation; writing – review and editing. **Marcel Arnold:** Validation; writing – review and editing. **Heinrich Mattle:** Conceptualization; formal analysis; funding acquisition; methodology; supervision; validation; writing – review and editing. **Simon Jung:** Conceptualization; formal analysis; funding acquisition; methodology; supervision; validation; writing – review and editing. **Christoph J. Schankin:** Conceptualization; formal analysis; investigation; methodology; project administration; supervision; validation; writing – original draft; writing – review and editing.

ACKNOWLEDGMENT

Open access funding provided by Inselspital Universitatsspital Bern.

FUNDING INFORMATION

This study received research support from the Swiss Heart Foundation (FF21070).

CONFLICT OF INTEREST STATEMENT

Nathalie L. Sutter, Morin Beyeler, Thomas R. Meinel, and **Franz Riederer** have no conflicts to declare. **Adrian Scutelnic** and **Simon Jung** report research support from the Swiss Heart Foundation. **Urs Fischer** reports consulting for Medtronic, Stryker, and CSL Behring, and serves on advisory boards for Portola/Alexion (money paid to institution). **Marcel Arnold** reports personal fees from AstraZeneca, Bayer, Bristol Myers Squibb, Covidien, Daiichy Sankyo, Medtronic, Novartis, Pfizer, and Amgen. **Heinrich P. Mattle** reports grants from Abbott for the PC and PRIMA trials and from Cerenovus for the ARISE studies, and personal and speaker fees from Cerenovus, Bayer, Servier, Medtronic, and Stryker. **Christoph J. Schankin** reports consulting, advisory boards, speaker, and travel support for/from Novartis, Eli Lilly, TEVA Pharmaceuticals, Allergan, Almirall, Amgen, Lundbeck, MindMed, Grünenthal and part-time-employment at Zynnon.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Scutelnic A, Sutter NL, Beyeler M, et al. Characteristics of acute ischemic stroke and unusual aura in patients with migraine with aura. *Headache*. 2024;00:1-6. doi:10.1111/head.14682