Factors associated with migraine aura-like symptoms in acute ischemic stroke

Adrian Scutelnic[1], Lucie Justus[1], Mattia Branca[2], Thomas R Meinel[1], Morin Beyeler[1], Norbert Silimon[1], Boudewijn Drop[1], David Seiffge[1], Urs Fischer[1,3], Marcel Arnold[1], Heinrich P Mattle[1], Christoph J Schankin[1], Simon Jung[1]

[1] Department of Neurology, Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland

[2] Clinical Trials Unit Bern, University of Bern, Bern, Switzerland

[3] Department of Neurology and Stroke Centre, University Hospital Basel and University of Basel, Basel, Switzerland

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Corresponding Author:

Adrian Scutelnic, MD

Department of Neurology

Inselspital, Bern University Hospital

University of Bern

Freiburgstrasse

CH-3010 Bern, Switzerland

Email: adrian.scutelnic@insel.ch

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List of abbreviations

IS Ischemic stroke

MA Migraine aura

AHA/ASA American Heart Association/American Stroke Association

ICHD International Classification of Headache Disorders

PFO Patent Foramen Ovale

PCA posterior cerebral artery

MCA middle cerebral artery

CSD cortical spreading deploarization

Introduction

Since Charles Miller Fisher pointed out the difficulties of clinically differentiating arteriosclerotic ischemia from migraine accompaniments more than 50 years ago,[1] only few small case series have been published depicting patients with confirmed ischemic stroke (IS) with symptoms similar to those of migraine aura (MA).[2,3,4] Nevertheless, the misdiagnosis of IS as MA is, unfortunately, not uncommon. In a recent prospective cohort study, 11% of patients clinically diagnosed with MA had an acute IS.[5] Identifying factors that influence the type of symptoms during an ischemic cerebral event might help in the clinical assessment of the origin of symptoms. This is particularly important since the history of symptoms was shown to be nondiscriminatory.[6,7] However, there is a lack of data on clinical factors associated with migraine-like symptoms in incipient IS.

The aim of this study was to identify factors associated with MA like symptoms in patients with IS. We hypothesize that patient- and stroke-related characteristics influence the type of symptoms at IS onset.

Methods

For this cross-sectional observational study, we interviewed patients with IS treated at our comprehensive Stroke Center or outpatient clinic between 03/2019 and 08/2021, using a structured questionnaire, as previously reported.[6] Inclusion criteria were: a) confirmed diagnosis of acute IS according to 2013 American Heart Association/American Stroke Association (AHA/ASA) definition requiring presence of ischemic lesion on neuroimaging,[8] b) occurrence of IS within six months prior to study inclusion, and c) age > 18 years. Excluded were patients with significant cognitive deficits, precluding a useful interview.[6] Data regarding co-morbidities, risk factors, location of the IS and stroke etiology was taken from discharge letters. The interviews were conducted after diagnosis of the IS. In our clinic, an emergency MRI is performed systematically in every patient with acute neurological symptoms, even in the setting of symptoms suggestive of MA.

Definitions

Migraine-like IS was defined as IS with symptoms fulfilling the C-criterion for MA of the International Classification of Headache Disorders, 3rd edition (see **Table 1**).[9] IS with classic symptoms was defined as IS not fulfilling the C-criterion for MA. The C-criterion was considered fulfilled when three of the six characteristics of the criterion were fulfilled (**Table 1**).[9] The presence of headache during wake-up was considered as fulfilled C6 characteristic in patients with wake-up IS. MA was spontaneously reported by the patients during the interview and the diagnosis was verified according to the current criteria.[9] Diabetes mellitus was defined as HbA1c >6.5%, arterial hypertension as antihypertensive treatment blood or pressure of 140/90mmHg or higher and dyslipidemia as ongoing lipid-lowering treatment or LDL>2.6mmol/l.

Data analysis

Given the lack of data on the frequency of migraine-like symptoms in IS, no prior study-size calculation was performed. The data analysis was performed in STATA/MP 16.0, Statacorp LCC. Descriptive statistics to compare the migraine- and stroke-like groups were used. Categorical variables are presented as counts and 95% confidence intervals (CI). Categorical variables were compared using the Chi-square or Fischer's exact test, as appropriate and continuous variables using the Mann-Whitney U test. To investigate the interaction between selected variables and ICHD-3 C-criterion, multivariable logistic regression was performed. For the logistic regression, variables which in univariate analysis had a *P*-value of <0.2 were included. Selected variables were selected among baseline characteristics, location of the IS and IS etiology. Sex was included in the model given its pathophysiological link to the susceptibility to cortical spreading depression (CSD).[10] In case of IS in multiple territories, each territory was counted separately. A *P*-value of <0.05 was considered statistically significant. In case of missing parameters, valid values and percentages were reported.

Ethics

This study has been approved by the local ethics committee (2018-02258). Informed consent was obtained from all participants prior to the interview.

Results

431 patients with IS were included, 172 were females (39.9%), 81 (18.8%) had wake-up IS, and the mean age was 60 (SD+/-13). The interviews were performed after a median (IQR) of 2 (1-3) days after the IS.

In 170 (39.4%) of 431 patients the history of symptoms fulfilled the C-criterion for MA (**Table 1**). There was no difference of proportions of fulfilled C-criterion between wake-up and non wake-up IS (OR 1, 95%CI 0.59-1.68) **(Table 2)**.

In univariate analysis, factors associated with migraine-like IS were younger age (mean age 66 vs 71.5 years, $P_{\text{Mann-Whitney-U}}<0.001$), co-morbid MA (OR 8.66, 95%CI 2.44-46.64), IS in the posterior cerebral artery (PCA) territory (OR 2.08. 95%CI 1.16-3.72) and patent foramen ovale (PFO) as IS aetiology (OR 2.65, 95%CI 1.07-6.56) (**Table 2**).

On the other hand, significantly less patients with migraine-like IS had arterial hypertension (OR 0.57, 95%CI 0.35-0.95) and diabetes mellitus (OR 0.57, 95%CI 0.32-0.99), and the IS was less often located in the middle cerebral artery (MCA) territory (OR 0.53, 95%CI 0.35-0.81).

One hundred seventeen (27%) of 431 had headache at IS onset. There were no significant differences of headache characteristics between patients with migraine-like and classic IS symptoms (**Table 3)**. For the distribution of symptoms, see **Table 4**.

In multivariable logistic regression only age (per year aOR 0.97, 95%CI 0.95-0.99) and IS in the MCA-territory as compared to IS outside the MCA-territory (aOR 0.44, 95%CI 0.2-0.94) remained significantly but negatively associated with migraine-like IS (**Supplemental Table**).

Discussion

The main finding of our study is the influence of patient-related characteristics on the type of symptoms at onset of IS. Age, prior diabetes mellitus, arterial hypertension and co-morbid MA as well as stroke-related characteristics such as location in the MCA and PCA territory, but also certain stroke etiologies differed in migraine-like IS compared to IS with classic symptoms in univariate analysis. However, after multivariable analysis, only younger age remained associated with migraine-like IS, while IS in the MCA territory was more likely to present as classic IS.

The association of younger age with ischemia-induced migraine-like symptoms is in-line with previous experimental reports on the influence of age and age-related mechanisms on the propagation velocity of CSD.[11] Older age was shown to be associated with a decline in CSD velocity in experimental animals, possibly explaining the lower rate of migraine-like IS with increasing age in our study.

Both CSD and thrombus migration, likely causing spreading and successive symptoms, have been reported in MCA-strokes.[12,13] Therefore, the negative association of the infarction in the MCA territory with migraine-like IS is unexpected. It may, however, be explained by a lower neuronal and higher relative neuroglia density of the brain parenchyma supplied by the carotid compared to the vertebrobasilar system.[14] In experimental primates, it has been shown that there is a gradient between the posterior and anterior parts of the brain in terms of the density of neurons relative to neuroglia: the primary visual cortex has the highest, the frontal cortex the lowest. Because neuroglia plays an important role in limiting the spread of CSD, our results could be explained by better neuroglial control of ischemia-induced CSD in anterior brain regions.[15]

In patients with headache at IS onset, we found no differences of the headache features between those with migraine-like and classic IS symptoms. This finding is counterintuitive, since migrainous features of headache were expected to be more frequent in stroke patients with migraine-like symptoms. In patients with MA, selectively inhibiting CSD does not influence migraine headache attacks, while it reduces the number of aura attacks.[16] Therefore, although it might explain migraine-like symptoms, CSD might not mediate migrainous features of headache in IS.

We found a high rate of fulfilled C-criterion in incipient acute IS (39.4%). These findings confirm the validity of the recently proposed clinical entity of "symptomatic migraine aura", specifically of symptomatic ischemia-induced MA.[17]

One of the strengths of our study is the large study population. The interviews were performed soon after the stroke happened, minimizing the risk of recall bias. Also, the interviews were performed by study investigators, minimizing the risk of misinterpreting the questions of the questionnaire. In addition, all patients were confirmed to have a diagnosis of acute IS according to the 2013 AHA/ASA definition requiring presence of an ischemic lesion on neuroimaging, leaving no ambiguity regarding the ischemic etiology of symptoms. Our study has also limitations. We did not assess the cognitive status of included patients. However, we included patients with whom an interview was possible, based on the general impression of the investigator. The results are not generalizable to patients with severe IS, since most included patients had minor stroke. We did not screen for migraine in stroke patients, which might have led to underestimating the impact of co-morbid migraine on symptom type during the IS. We included patients with IS in multiple territories, which might confound the association of certain IS territories with migraine-like symptoms. However, by using the method of multivariable logistic regression, we attempted to adjust for the interaction between different IS locations.

In conclusion, patient- and IS-related characteristics might influence the type of symptoms in IS. In multivariable analysis, younger age was associated with migraine-like IS, while IS in the MCA territory was more likely to present as classic IS.

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Table 1. The ICHD 3rd edition criterion C for migraine aura

C. At least three of the following six characteristics:	Fulfilled in 170/431 (39.4%), n/170 (%)
1. at least one aura symptom spreads gradually over ≥ 5 minutes	87 (51)
2. two or more aura symptoms occur in succession	114 (67)
3. each individual aura symptom lasts 5-60 minutes[1]	43 (25)
4. at least one aura symptom is unilateral[2]	166 (98)
5. at least one aura symptom is positive[3]	115 (68)
6. the aura is accompanied, or followed within 60 minutes, by headache*	74 (44)

*in wake-up patients, headache was assessed if present during wake-up

1. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.
3. Scintillations and pins and needles are positive symptoms of aura.

Table 2. Baseline characteristics, imaging, acute treatment and etiologies of ischemic stroke patients

		ICHD-3 C criterion not fulfilled (n=261)	ICHD-3 C criterion fulfilled (n=170)	*P* value	unadjustedOR (95%CI)*
Baseline					
Age (years, SD)		71.5 (11.2)	66 (14.7)	**<0.001**	
Female sex n/N (%)		98/261 (37.6)	74/170 (43.5)	0.21	1.28 (0.84-1.93)
Wake-up stroke n/N(%)		49/261 (18.8)	32/170 (18.8)	0.98	1 (0.59-1.68)
NIHSS, median (IQR)		1 (0-3)	1 (0-3)	0.97	
Body mass index, kg/m^2 (IQR)		26.1 (23.4-29.3)	26.2 (23.7-29.5)	0.97	
Prior ischemic stroke n/N (%)		53/233 (22.7)	33/151 (21.9)	0.84	0.94 (0.56-1.59)
Prior TIA n/N (%)		13/233 (5.6)	7/151 (4.6)	0.68	0.82 (0.27-2.28)
Prior ICH n/N (%)		4/233 (1.7)	3/151 (2)	0.85	1.16 (0.16-6.96)
Prior arterial hypertension n/N (%)***		186/233 (79.8)	105/151 (69.5)	**0.02**	**0.57 (0.35-0.95)**
Prior diabetes mellitus n/N (%)***		58/233 (24.9)	24/151 (15.9)	**0.03**	**0.57 (0.32-0.99)**
Prior hyperlipidemia n/N (%)***		180/233 (77.3)	116/151 (76.8)	0.92	0.97 (0.58-1.64)
Active smoking n/N (%)		65/233 (27.9)	38/151 (25.2)	0.56	0.86 (0.52-1.41)
Prior congestive heart failure n/N (%)		44/233 (18.9)	27/151 (17.9)	0.8	0.93 (0.52-1.63)
Prior peripheral artery disease n/N (%)		10/233 (4.3)	12/151 (7.9)	0.13	1.92 (0.73-5.11)
Antiplatelets pre-stroke n/N (%)‡‡‡		90/237 (37.9)	59/151 (39)	0.82	1.04 (0.67-1.62)
Vit K antagonist pre-stroke n/N (%)		8/237 (3.4)	1/151 (0.7)	0.08	0.19 (0.004-1.45)
DOAC pre-stroke n/N (%)**		17/237 (7.1)	6/151 (3.9)	0.19	0.53 (0.16-1.46)
Parenteral anticoagulation pre-stroke n/N (%)		3/237 (1.3)	5/151 (3.3)	0.16	2.67 (0.5-17.4)
Antihypertensive treatment pre-stroke n/N (%)		139/237 (58.6)	81/151 (53.6)	0.33	0.81(0.52-1.25)
Lipid lowering drugs pre-stroke n/N (%)		85/237 (35.9)	43/151 (28.5)	0.13	0.71 (0.44-1.13)
Oral contraceptive use (women only) n/N (%)		3/98 (3.1)	7/74 (9.4)	0.07	3.3 (0.71-20.39)
Known migraine with aura‡		3/260 (1.2)	17/170 (10)	**<0.001**	**8.66 (2.44-46.64)**
Imaging					
Acute imaging type n/N (%)	CT	22/261 (8.4)	11/170 (6.5)	0.45	0.76 (0.32-1.7)
	MRI	239/261 (91.5)	159/170 (93.5)		
Location of the ischemic lesion n/N (%)	MCA	181/261 (69.3)	93/170 (54.4)	**0.002**	**0.53 (0.35-0.81)**
	ACA	11/261 (4.2)	11/170 (6.5)	0.29	1.57 (0.6-4.09)
	PCA	28/261 (10.7)	34/170 (20)	**0.007**	**2.08 (1.16-3.72)**
	Vertebrobasilar†††	85/261 (32.6)	67/170 (39.4)	0.14	1.34 (0.88-2.05)
Etiology TOAST n/N (%)	Cardiac embolism	53/230 (23)	23/149 (15.4)	0.07	0.6 (0.33-1.07)
	Cervical artery dissection	2/230 (0.9)	2/149 (1.3)	0.64	1.55 (0.11-21.58)
	LAA	39/230 (17)	31/149 (20.8)	0.34	1.28 (0.73-2.24)
	More than one possible etiology	7/230 (3)	10/149 (6.7)	0.09	2.29 (0.76-7.25)
	Other determined etiology	9/230 (3.9)	10/149 (6.7)	0.22	1.76 (0.62-5.04)
	PFO	8/230 (3.5)	13/149 (8.7)	**0.02**	**2.65 (1.07-6.56)**
	Small vessel disease	18/230 (7.8)	17/149 (11.4)	0.23	1.51 (0.70-3.23)
	Unknown etiology despite complete evaluation‡‡	36/230 (15.7)	22/149 (14.8)	0.81	0.93 (0.49-1.71)

IQR: interquartile range; SD: standard deviation; NIHSS: national institutes of health stroke scale; CT: computed tomography; MRI: magnetic resonance imaging; TOAST: Trial of Org 10172 in Acute Stroke Treatment; PFO: patent foramen ovale; LAA: large artery atherosclerosis; TIA: transient ischemic attack; MCA: middle cerebral artery; PCA: posterior cerebral artery including diencephalon

*OR ICHD-3 fulfilled C criterion vs not

‡migraine with aura according to the international classification of headache disorders (ICHD-3) criteria; †only patients with vascular imaging included; ††only patients with perfusion imaging included; ††† vertebrobasilar include brainstem and cerebellum; ‡‡ assessed three months after the stroke; unknown etiology with incomplete evaluation n=80

‡‡‡ Antiplatelets: Aspirin n=125, Clopidogrel n=24

** DOAC: Rivaroxaban n=12, Edoxaban n=1, Dabigatran n=3, Apixaban n=7

*** Diabetes mellitus defined as HbA1c >6.5%, arterial hypertension defined as antihypertensive treatment or blood pressure of 140/90mmHg or higher, dyslipidemia defined as lipid-lowering treatment or LDL>2.6mmol/l

Table 3. Differences in headache characteristics between patients with stroke-like and migraine-like ischemic stroke

	ICHD-3 C criterion not fulfilled (261)	ICHD-3 C criterion fulfilled (170)	*P* value
Headache N (%)	43/261 (16.5)	74/170 (43.6)	<0.001
Character			
Pulsating n/N (%)	4/43 (9.3)	8/74 (10.8)	0.53
Throbbing n/N (%)	2/43 (4.7)	3/74 (4.5)	0.6
Shooting/Stabbing n/N (%)	10/43 (23.2)	19/74 (25.7)	0.77
Dull/Pressing n/N (%)	29/43 (67.4)	52/74 (70.3)	0.74
Aggravation upon movement n/N (%)	10/43 (23.3)	20/74 (27)	0.65
Photophobia n/N (%)	5/43 (11.6)	17/74 (22.9)	0.13
Phonophobia n/N (%)	3/43 (6.9)	10/74 (13.5)	0.26
Nausea n/N (%)	12/43 (27.9)	23/74 (31)	0.71

Table 4. Distribution of symptoms in patients with stroke-like and migraine-like ischemic stroke

Symptoms	ICHD-3 C criterion not fulfilled (261)	ICHD-3 C criterion fulfilled (170)	*P* value
Visual n (%)	31 (11.8)	65 (38.2)	<0.001
Speech n (%)	140 (53.6)	98 (57.6)	0.41
Sensory n (%)	69 (26.4)	115 (67.6)	<0.001
Motor n (%)	140 (53.6)	109 (64.1)	0.03

Supplemental Table 1. Results of the multivariable logistic regression

	OR (95%CI)	*P*-value
Age	0.97 (0.95-0.99)	**0.005**
Sex	0.77 (0.49-1.21)	0.26
Prior arterial hypertension	0.94 (0.52-1.69)	0.83
Prior diabetes mellitus	0.58 (0.32-1.05)	0.07
Prior peripheral artery disease	2.29 (0.91-5.78)	0.07
Parenteral anticoagulation pre-stroke	4.18 (0.83-20.94)	0.08
Vitamin K antagonist pre-stroke	0.33 (0.03-2.79)	0.31
DOAC	0.95 (0.34-2.64)	0.92
Lipid lowering drugs pre-stroke	0.81 (0.49-1.35)	0.44
Known migraine with aura	0.89 (0.22-3.64)	0.87
MCA	0.44 (0.2-0.94)	**0.03**
PCA	1.71 (0.89-3.27)	0.10
Vertebrobasilar	0.63 (0.3-1.32)	0.22
Cardiac embolism	0.81 (0.45-1.47)	0.49
More than one possible etiology	2.01 (0.70-5.74)	0.19
PFO	1.06 (0.36-3.16)	0.90

MCA: middle cerebral artery; PCA: posterior cerebral artery including diencephalon, PFO patent foramen ovale, DOAC: direct oral anticoagulants