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The "index vein" as a sign for migraine aura in the emergency setting

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Abstract

Background and objectives To assess the usefulness of the "index vein" for making the diagnosis of migraine aura.
Methods 400 patients were included when they: i) presented with an acute neurological deficit, ii) had a brain MRI, and iii) had a discharge diagnosis of migraine aura, ischemic stroke, epileptic seizure or controls (n = 100 per group).
Results Compared to stroke (2%), epileptic seizure (4%) and controls (1%), the index vein is more prevalent in migraine aura (17%, $p < 0.001$). The index vein is highly specific for migraine aura (specificity 97%, 95% CI 95–99). The index vein has a positive predictive value for the diagnosis of migraine aura of 70% (95%CI 48–87). The index vein-score has the ability to diagnose migraine aura with a sensitivity of 94% (95%CI 87.4–97.8) and specificity of 73.5% (95%CI 66.8–79.5) at a cut-off of 4 points.
Discussion The index vein serves as a good biomarker for migraine aura in the emergency setting.

Keywords

Index vein, migraine aura, stroke, epilepsy

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Introduction

Neurologists are often confronted with transient neurologic deficits of acute onset. In the absence of positive findings for stroke in MRI, mimics, such as migraine aura or epileptic seizures have to be considered. Radiologic markers confirming the diagnosis of migraine aura, such as the "index vein" (IV) (1), would greatly facilitate the algorithm in the emergency room as well as the subsequent after-care. The IV is defined as a two-fold increase in diameter of a vein in susceptibility-weighted imaging (SWI) compared to contralateral side, in a brain area which correlates with the neurologic deficits. The objective of this study was to assess the usefulness of the IV for making the diagnosis of migraine aura. We hypothesized that the IV occurs more often in migraine aura compared to epileptic seizure or ischemic stroke. Further, we aimed at increasing the accuracy of the clinical diagnosis by defining a score based solely on history and the presence of IV.

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Methods

This retrospective case-control study was approved by the Bern cantonal ethics committee (2020-00115). The IV was defined according to our previous work (1): a single prominent vein in susceptibility-weighted MRI draining the cortical area of the neurological deficit in the absence of diffusion abnormality and vessel occlusion on angiography (example in Figure 1). Four hundred patients (n = 100 per group, consecutive for each group) were included, when they: i) presented at our emergency department with an acute neurological deficit, ii) had brain MRI either when symptoms were still present or within eight hours after the cessation of symptoms, and iii) had a discharge diagnosis of migraine aura (68 female, i.e. 68% female, mean age 39 ± 15), ischemic stroke (31 female, mean age 66 ± 14), epileptic seizure (54 female, mean age 59 ± 19) or none of these (controls, 55 female, mean age 61 ± 13). The cut-off of eight hours has been chosen based on findings of a previous cohort, demonstrating persistent dilated veins within this timeframe in patients with migraine aura (2). Clinical information and final diagnoses were taken from the discharge letters. Diagnoses were made by experienced neurologists in the emergency room who have been trained to identify migraine aura according to the International Classification of Headache Disorders (3), ischemic stroke according to the 2013 American Heart Association/American Stroke Association (AHA/ASA) definition (4). The epileptic seizures were reported according to the 2017 International League Against Epilepsy (5) classification. No imputation for missing data was done. AS and CJS had access to all clinical and radiological data.

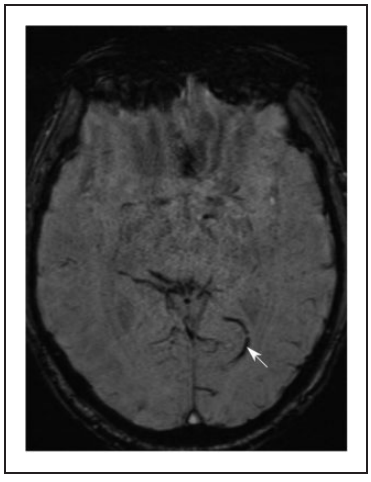

Figure 1. Example of an index vein (IV), i.e. a single prominent vein in susceptibility weighted imaging draining the area of the neurological deficit. The patient had a history of migraine with visual aura. He experienced dysphasia for about 20 minutes followed by right-sided scintillating scotoma that started in the center of the visual field and spread centrifugally over 30 minutes to the periphery. A head MRI was done in the emergency setting revealing an IV pointing to the visual cortex (arrow), without further pathologic findings.

The IV was assessed by two senior neuroradiologists (VP, NS) blinded to the diagnosis.

In R (version 3.6.1, R Foundation, Vienna, Austria), we performed descriptive statistics, Pearson's chi-squared test or Fisher exact test, as appropriate. For the primary analysis, we compared the frequency of IV between all four groups and calculated accuracy measures. For the clinical score, we: i) focused on the IV and variables that could be assessed by taking history and ii) compared the migraine group with stroke and epileptic seizure combined (no migraine group); controls were excluded, as they were not part of the clinical differential diagnosis. The variables that differed significantly were used for bootstrap model selection and validation. Based on the coefficient, the contribution of each variable to the score was defined (weighted IV-score, using the Sullivan's scoring system). Accuracy of the score was calculated using area under the receiver operating characteristic curve (auROC). Upon reasonable request study data will be made available.

Results

Compared to stroke (2%), epileptic seizure (4%) and controls (1%), the IV was more prevalent in migraine aura (17%, $p < 0.001$, chi-square test). The Cohen's kappa for the assessment of IV was 0.65. Although the sensitivity was low (17%), we found the IV to be highly specific for migraine aura (specificity 97%, 95% CI 95–99). The IV has a positive predictive value for the diagnosis of migraine aura of 70% (95%CI 48–87), higher compared to stroke (8%, 95%CI 1–27), epileptic seizure (16%, 95%CI 4–37) and controls (4%, 95%CI 0.1–21). In an exploratory manner, we compared patients with migraine aura without IV to those with IV. The absence of weakness ($p = 0.03$), presence of sensory symptoms ($p = 0.03$), presence of speech disturbance ($p = 0.006$) and non-smoking ($p = 0.02$) were associated with IV (Chi square). The symptoms of patients with migraine with aura with and without IV are presented in Table 1.

Table 2 shows the clinical characteristics of the three groups that can be obtained solely from taking history in the emergency situation (controls excluded as not part of the clinical differential diagnosis). Chi-square followed by bootstrap modelling identified the parameters listed in Table 2 as discriminating between the migraine and no migraine group. Based on this data, the IV-score was defined as the sum of a combination of these parameters weighted by the bootstrap model coefficient: presence of IV (= 1 point) + presence of

Table 1. Symptoms of patients with migraine with aura with and without index vein (IV).

	no IV (N = 83)	IV (n = 17)	P-value (Chi square or Fischer's exact test)
Visual disturbance, n (%)	55 (66)	10 (59)	0.55
Sensory disturbance, n (%)	40 (48)	13 (76)	0.03
Weakness, n (%)	18 (22)	0 (0)	0.03
Speech disturbance, n (%)	29 (35)	12 (71)	0.006
Coordination disturbance, n (%)	2 (2)	2 (12)	0.13
Vertigo, n (%)	13 (16)	1 (6)	0.45
Double vision, n (%)	1 (1)	0 (0)	0.83
Headache, n (%)	59 (71)	15 (88)	0.14

Table 2. Clinical characteristics of study population (n = 100 per group unless otherwise specified). The control group (n = 100) had clinical symptoms that were not in the differential diagnosis of migraine aura and therefore is not shown here for the sake of clarity. In the control group, only one patient (1%) had an IV.

		No migraine		Migraine vs. no migraine				
					Bootstrap model selection and validation			
	Migraine	Stroke	Epilepsy	Chi-square p-value	Coefficient (95%-CI)	OR (95%-CI)	P-value	Score
Presence of Index Vein	17	2	4	<0.001	1.98 (0.39–3.57)	7.24 (1.48–35.54)	0.015	1
History of symptoms								
Visual symptoms	65	20	8	<0.001	2.86 (1.99–3.73)	17.48 (7.33–41.67)	<0.001	1
Sensory symptoms	53	50	16	0.001	1.97 (1.12–2.83)	7.19 (3.05–16.91)	<0.001	1
Motor symptoms	18	55	67	<0.001	2.01 (1.14–2.89)	7.50 (3.13–17.94)	<0.001	1
Speech disturbance	41	64	33	0.269				
Coordination problems	4	42	5	<0.001	3.34 (1.82–4.86)	28.18 (6.16–128.95)	<0.001	2
Loss of consciousness	1	0	56	<0.001				
Vertigo	14	30	5	0.439				
Double vision	1	8	0	0.280				
Cardiovascular risk factors								
Hypertension	15	64	46	<0.001	2.91 (1.95–3.87)	18.33 (7.03–47.76)	<0.001	1
Dyslipidemia	9	44	18	<0.001				
Diabetes	6	23	16	0.002				
Smoking	17	32	8	0.532				
Family history of stroke/MI	0	5	1	0.184				
Obesity	1	10	3	0.040				
Atrial fibrillation	2	12	5	0.041				
Kidney failure	0	7	5	0.010				

visual symptoms (=1 point) + presence of sensory symptoms (=1 point) + absence of motor symptoms (=1 point) + absence of coordination problems (=2 points) + absence of history of hypertension (=1 point). For the distinction between migraine and no migraine, the IV-score has an auROC of 0.927. A score of 4 has the ability to diagnose migraine aura with a sensitivity of 94% [95%CI 87.4–97.8], a specificity of 73.5% [66.8–79.5], as well as a positive and negative predictive value of 63.9% [55.6–71.7] and 96.1% [91.7–98.5]. Exclusion of the IV from the score did not substantially change sensitivity (93.0% [86.1–97.1]), specificity (74.0% [67.3–79.9]), positive and negative predictive value (64.1% [55.8–71.9] and 95.5% [90.9–98.2]).

Discussion

This study demonstrates a high specificity of the IV for migraine aura compared to stroke and epileptic seizure in patients with an acute neurological deficit. This is important since it confirmed the hypothesis of a recent case series that defined the IV in six patients with migraine aura (1) suggesting that it might be

a biomarker for migraine aura. A prominent single vein on SWI draining the cortical area of symptom origin would be more likely caused by migraine aura than by epileptic seizure or stroke. All three conditions result in a relative increase of deoxyhemoglobin levels in the draining veins, which then will appear prominent and hypointense on SWI (6). However, only cortical spreading depression, the slowly propagating wave of abnormal neuronal excitation followed by prolonged inhibition that is considered to be the correlate of migraine aura (7), would result in a single prominent vein. In contrast, we would expect a much larger territory to be affected in ischemia or epileptic seizure, where propagation is much faster or almost instantaneous, as previously discussed (1).

Based on our data, patients with an acute neurological deficit who have MRI during symptoms or within eight hours after symptoms have stopped, should be investigated for the presence of an IV. In the absence of diffusion abnormalities or vascular occlusions, the IV strongly supports the diagnosis of migraine aura. For use in clinical routine, however, a limitation of the IV alone is its low sensitivity. In contrast, the proposed IV-score, i.e. a combination of clinical information by history and unremarkable neuroimaging except for the presence of an IV, has a high sensitivity and specificity, and might be helpful to reassure the physician that the deficit was caused by migraine aura. This might be useful especially when migraine aura is atypical. Migraine aura characteristics, such as positive or spreading symptoms alone are not specific, as they have been observed in ischemic stroke confirmed by imaging (8,9). They also may contain negative symptoms (10) or last longer than the 60 minutes allowed by the ICHD-III criteria (3,10), which brings into consideration cerebral ischemia or epileptic seizure with the resulting subsequent examinations, intake of antithrombotic or anti-seizure treatment, and consequences for the ability to drive. Remarkably, in patients with migraine with aura, non-smoking was associated with the presence of IV. The differences in smoking and non-smoking patients with migraine is possibly explained by changes in the cerebral circulation caused by smoking (11). However, a direct causal inference cannot be determined from our study.

A strength of our study is the large number of subjects investigated in the acute clinical setting. At our emergency room, all patients are assessed by neurologists, who are experienced in making accurate diagnoses of migraine, epileptic seizure, and stroke suggesting high data quality. Further, the application of the bootstrap mechanism allowed both, derivation of the score and confirmation in a large cohort of patients. A limitation is the retrospective study design and that the IV-score was not the primary endpoint. Also, the history was likely not highly systematic. We could not assess whether the migraine aura was typical or atypical or how long it has lasted, which might have led to a selection bias of patients with atypical aura, since these are more likely to present to the emergency department. Although not required by the definition of IV (1), there might be an interaction between the presence of an IV and perfusion changes, especially in patients with focal epileptic seizures. The low number of patients with perfusion done in our seizure group did not allow the investigation into such possible interaction. A limitation of the IV-finding is its lack of influence on the IV-score. However, given its high specificity, the presence of IV strongly supports the diagnosis of migraine aura in the clinical setting. We propose looking for the IV and investigating the IV-score prospectively in the clinical setting to confirm our findings.

In conclusion, when present, the IV serves as a good biomarker for migraine aura in the emergency setting. A simple to implement score based on history and information about the presence of the IV may help to diagnose migraine with aura with excellent diagnostic accuracy.

Clinical Implications

- The index vein is a highly specific sign for migraine aura.
- The index vein-score, which includes the presence of index vein, has the ability to diagnose migraine aura with high sensitivity and specificity.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: AS, VP, LS, SJ, MBr, MBe, NS, RW: none.

UF: Consulting for Medtronic, Stryker, CSL Behring. Advisory boards for Portola/Alexion (money paid to institution).

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Ethic approval and patient consent

This study was approved by the cantonal ethics committee Bern (2020-00115). All participants were included based on the general consent procedure at our hospital.

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