Migraine Aura mimicking Stroke in Code Stroke. Analysis of diagnostic prediction models.

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Abstract

Background: Differences between migraine with aura (MA) mimicking stroke and ischemic strokes were analyzed to create a predictive diagnostic model.

Methods: Prospective cohort of code strokes attended between January 2005 and June 2020 in a tertiary hospital evaluated by a vascular neurologist. Data recorded included: Place of activation, demographics, vascular risk factors, vitals, initial blood test (glucose, blood count, electrolytes, coagulation times, D-dimer, fibrinogen and C-reactive protein), initial NIHSS, door-to-onset time, and door-to-needle time. After the vascular study, diagnosis of ischemic stroke or MA was registered. Multivariate logistic regression analyses were performed to create a predictive model. Discrimination and calibration performance were assessed. A secondary aim was to describe detailed clinical and radiological data of MA cases in order to identify new predictive factors that could be used in future studies.

Results: Of 3140 code strokes attended, 2424 (77.2%) were ischemic strokes and 34 (1.1%) were MA. Migraine cases were younger, more frequently females and with low prevalence of vascular risk factors. Initial NIHSS was lower in MA cases, but no differences were seen in fibrinolysis rate (30%). Blood test showed lower levels of glucose, D-dimer, and fibrinogen in MA cases. Multivariate model showed and independent association for ischemic stroke with age [OR, (95%CI):1.09, (1.07-1.12, p<0.001], male sex [OR, (95%CI):4.47, (3.80-5.13), p<0.001], initial NIHSS [OR, (95%CI):1.21, (1.07-1.34), p<0.01], and fibrinogen levels [OR, (95%CI):1.01, (1.00-1.01), p<0.05]. A model including sex and cut-off points (age>65, NIHSS>6, and fibrinogen>400mg/dL) showed a good global discrimination capacity (AUC = 0.897) but a good calibration only for extreme predicted probabilities (>98% in ischemic strokes or < 10% in MA). We did not find any differential clinical or radiological factor that could be exclusive of MA.

Conclusions: A predictive model including age >65, men sex, NIHSS >6 and fibrinogen >400 mg/dL showed a good discrimination, but low calibration performance to distinguish between MA and ischemic stroke. Future studies should involve migraine biomarkers in order to improve clinical decision making.

Background

Migraine with aura (MA) is a frequent stroke simulator. A recent metanalysis showed that migraine represents 1.18% of all emergency stroke unit evaluations, being the third cause of stroke mimic after epileptic seizures and conversion disorder [1]. It represents up to 18% of stroke mimics that receive fibrinolytic treatment and although the risks of iatrogenic complications might be low, some bleedings have been described in these patients [1–3].

Typically, symptoms of MA are progressive and include visual, sensory or language impairment [4]. Nevertheless, miseducation about aura, clinical variability between episodes and sudden onset might rise the suspicion of a stroke.

Despite the fact that MA continues to be a diagnostic challenge in the code stroke, few studies have analyzed MA mimicking ischemic strokes in order to improve selection for reperfusion therapies and avoid misdiagnosis [5].

Therefore, the aim of this study was to analyze the initial clinical and blood data of a large cohort of code strokes in order to find differences between patients with final diagnosis of MA and patients with ischemic stroke to create a diagnostic predictive model. As a secondary objective, we reviewed clinical and radiological data of MA cases in order to find out potential different traits that could be considered in future studies.

Material And Methods

Study population

We conducted a prospective cohort study of code stroke cases (patients transferred to the emergency department following pre-hospital or in-hospital code stroke activation) between January 2005 and June 2020 in Hospital del Mar, the only hospital serving 320.000 inhabitants from two districts of Barcelona (Spain).

All cases were evaluated by the on-call vascular neurologist who confirmed code stroke activation, performed complete neurovascular study and indicated acute reperfusion therapies. Cases with code stroke deactivation in the initial evaluation were not registered. Cases with code stroke confirmation were registered in the prospective BASICMAR registry [6]: a continuous database of patients with acute stroke attended in our hospital that includes clinical and radiological data, blood biomarkers, and prognosis. Moreover, since 2016 all code stroke activations in our region are centrally recorded and final diagnosis of stroke mimic is also registered [7].

Neurovascular study and treatment protocol

Urgent neurovascular study included non-contrast brain CT (NCCT), blood test, electrocardiography study and chest X-ray. Head and neck vascular study was performed with 2D ultrasound. Since 2014, most cases underwent an institutional stroke imaging protocol: including NCCT, CT angiography (CTA) from aortic arch to vertex, and CT perfusion (CTP) with 8 cm of brain coverage. Color-coded perfusion maps showing cerebral blood volume (CBV), cerebral blood flow (CBF) and Tmax were generated with a commercially available software (AW Server. General Electric).

Blood test was performed at patient's arrival in the emergency room and included: complete blood count, glucose, electrolytes, coagulation times, D-dimer, fibrinogen, and C-reactive protein.

After completion of the neurovascular study, final diagnosis of ischemic stroke or migraine with aura according to the WHO and ICHD-III respectively was registered in the database [8, 9].

Variables registered

Clinical and demographic data were registered in a structured questionnaire that has been used in previous studies [6]. We included age, sex, vascular risk factors (hypertension, dyslipidemia, diabetes mellitus, smoking), alcohol overuse (defined as a daily ethanol intake higher than 30g), atrial fibrillation, previous stroke or transient ischemic attack (TIA), documented ischemic heart disease, peripheral artery disease, place of code stroke activation (outside hospital including street or patient home, primary care center, emergency department (ED), other hospital department), previous modified Rankin Scale (mRS), initial NIHSS, thrombolytic treatment, onset to door time (ODT), onset to needle time (ONT), vital signs at ED arrival (systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, temperature), initial blood test (glucose, D-dimer, fibrinogen, C-reactive protein (CRP), leucocyte count and international normalized ratio (INR))

Cases with MA were reviewed by two investigators (A.M. and A.S.) who additionally registered: family history of migraine; previous diagnosis and misdiagnosis of migraine with or without aura; type of symptoms: sensory positive (which include paresthesia/tingling, dysesthesia, allodynia, hyperalgesia or neuropathic pain) or sensory negative (defined as a deficit of sensory function such as hypoesthesia/numbness or anesthesia), motor, language, visual positive (simple or complex unformed or formed images perceived by the patient without a real stimulus, such as photopsia, scintillating/fortification scotoma) or visual negative (visual deficits, such as blind scotomas, hemianopsia), vertigo; symptom duration; headache associated to neurological symptoms (since beginning, after beginning, not present); first neuroimaging performed (NCCT, CTA, CTP), control neuroimaging performed (no, brain CT, MRI).

Statistical analysis

A bivariate analysis with descriptive statistics was performed to compare demographics, comorbidity, clinical, and blood data between patients with stroke and MA. Variables were reported according to their means and SD for continuous variables, and total number and percentages for categorical variables.

We then constructed a set of logistic regression models to understand which factors were independently associated with MA and allowed a better discrimination with stroke patients. In the first model we introduced those variables statistically associated (p-value < 0.05) with stroke in the univariate analysis, as long as there were at least 10 observations in the MA group (model 1). Since Hypertension/SBP and Diabetes mellitus/Glucose showed a moderate to high correlation, we only used quantitative variables to avoid concerning collinearity. We subsequently aimed to obtain a more parsimonious model by applying a forward stepwise variable selection according to p-values (model 2). Finally, in order to provide clinical insight and applicability, we dichotomized those variables associated with stroke that remained in model 2 after the stepwise selection. We used as cutoff the point that had the bigger area under the receiver operating curve for each variable included in model 2 (AUC) (model 3).

Cases with missing data were not imputed. Discrimination and Calibration ability for each model was quantified using the AUC and the Hosmer-Lemeshow test, respectively. The magnitude of error for

predicted probability was calculated with the Brier score. Analyses were performed with SPSS® statistical software (version 25) and R (version 4.1.0).

Results

During the study period a total of 3140 code strokes were activated by a vascular neurologist. Of them 504 (16.0%) were hemorrhagic strokes, 2424 (77.2%) were ischemic strokes, and 212 (6.8%) were diagnosed with stroke mimic. Among mimics, we found 34 patients (16.0% of the stroke mimics, 1.1% of the code strokes) with a final diagnose of MA and 178 (84.0%) patients with a non-MA stroke mimic. The study flowchart is summarized in Fig. 1.

Code stroke activations in primary care centers were more frequent in MA (11.8% vs 2.8%), whereas street/home activations were more frequent in ischemic strokes (29.4% vs 44.1%) p = 0.022.

Regarding baseline characteristics, patients with MA were younger [49.1 (SD: 14.8) years vs. 73.1 (SD: 13.3) years], were more frequently female (73.5% vs 47.9%), and had a lower previous mRS than ischemic stroke cases. Prevalence of vascular risk factors and cardiovascular disease was lower in MA except for smoking. This information is shown in Table 1. Globally, there were no differences in vital signs at arrival, except for SBP that was lower in MA. Initial NIHSS was lower in MA patients (median 2, p25-75: 1–4 vs 6, 3–15). About the parameters registered in the initial blood test, we found lower glucose, D-dimer and fibrinogen levels in MA patients. There were no differences neither in admission times nor in thrombolysis rate between MA and ischemic strokes (26% vs 28%).

Table 1
Clinical characteristics and bivariate comparison between migraine with aura patients and ischemic stroke.

n total = 2458	Migraine with aura (n = 34)	Ischemic stroke (n = 2424)	p
Mean age, years (SD)	49.12 (14.78)	73.07 (13.30)	**< 0.001***
Sex (female), n (%)	25 (73.5)	1160 (47.9)	**0.003***
Hypertension, n (%)	11 (32.4)	1811 (74.7)	**< 0.001**
Dyslipidemia, n (%)	10 (29.4)	1205 (49.7)	0.056
Diabetes mellitus, n (%)	4 (11.8)	776 (32.0)	**0.040**
Smoking, n (%)	12 (35.3)	568 (23.6)	0.243
Alcohol overuse, n (%)	0 (0)	360 (14.9)	**0.015**
Atrial fibrillation, n (%)	0 (0)	903 (37.3)	**< 0.001**
Previous stroke, n (%)	2 (5.9)	540 (22.3)	**0.022**
Ischemic heart disease, n (%)	1 (2.9)	414 (17.1)	**0.029**
Peripheral artery disease, n (%)	0 (0)	225 (9.3)	0.154
Place of activation, n (%)			**0.022**
• street	10 (29.4)	1064 (44.1)	
• primary care	4 (11.8)	68 (2.8)	
• emergency room	19 (55.9)	1170 (48.5)	
• admitted in the hospital	1 (2.9)	110 (4.6)	
previous mRS (med, q1-q3)	0, 0–0	0, 0–2	**< 0.001***
Initial NIHSS (med, q1-q3)	2, 1-4.25	6, 3–15	**< 0.001***
Thrombolytic treatment, n (%)	9 (26.5)	683 (28.2)	0.826
ODT, mean (SD) min	149.47 (147.95)	181.61 (291.82)	0.522
DNT, mean (SD) min	139.78 (65.61)	119.44 (53.50)	0.381
SBP†, mean (SD) mmHg	144.88 (26.85)	157.05 (31.04)	**0.014***
DBP†, mean (SD) mmHg	82.87 (12.98)	81.40 (16.54)	0.762
Heart rate, mean (SD) bpm	81.53 (15.96)	80.16 (18.94)	0.674

*: selected to multivariate analysis. Missing data in MA group (†): SBP, DBP, and fibrinogen 1; temperature 6. Missing data in ischemic stroke group (§): glucose 49; Ddimer 593; fibrinogen 593; CRP 515; leucocytes 51; INR 169.

n total = 2458	Migraine with aura (n = 34)	Ischemic stroke (n = 2424)	p
Temperature†, mean (SD) Celsius degrees	36.24 (0.55)	36.07 (0.59)	0.126
Glucose§, mean (SD) mg/dL	109.91 (34.74)	143.34 (60.80)	**< 0.001***
Ddimer§, mean (SD) mcg/L	407.05 (523.174)	837.52 (1202.38)	**< 0.001***
Fibrinogen†§, mean (SD) mg/dL	338.48 (84.04)	408.77 (117.21)	**< 0.001***
CRP§ mean (SD) mg/dL	0.61 (2.24)	1.33 (3.20)	0.192
Leucocyte count§, mean (SD) per µL	9665.00 (3194.75)	9620.67 (7736.78)	0.973
INR§, mean (SD)	1.08 (0.40)	1.76 (7.35)	0.591
*: selected to multivariate analysis. Missing data in MA group (†): SBP, DBP, and fibrinogen 1; temperature 6. Missing data in ischemic stroke group (§): glucose 49; Ddimer 593; fibrinogen 593; CRP 515; leucocytes 51; INR 169.			

Table 1 *(now placed at the end of the document text file) should be included here.*

MA prediction

In the first model we adjusted for all those variables showing a statistically significant effect on stroke in the univariate analysis. In this model we observed an independent association between stroke and age [OR, (95%CI):1.09, (1.07–1.12, $p < 0.001$], male sex [OR, (95%CI):4.47, (3.80–5.13), $p < 0.001$], initial NIHSS [OR, (95%CI):1.21, (1.07–1.34), $p < 0.01$], and fibrinogen levels [OR, (95%CI):1.01, (1.00-1.01), $p < 0.05$]. These results are displayed in Table 2.

Table 2
Regression Models. OR [95% CI]

	Model 1	Model 2	Model 3
Age	1.099 [1.068; 1.129]***	1.103 [1.076; 1.129]***	
Sex (male)	4.469 [3.805; 5.134]***	4.299 [3.666; 4.932]***	4.145 [3.551; 4.740]***
Previous mRS	1.266 [0.570; 1.963]		
NIHSS	1.212 [1.077; 1.347] ***	1.252 [1.123; 1.380] ***	
SBP (mmHg)	1.006 [0.992; 1.021]		
Glucose (mg/dL)	1.007 [0.995; 1.020]		
D-dimer (mg/dL)	1.000 [1.000; 1.001]		
Fibrinogen (mg/dL)	1.005 [1.000; 1.009] *	1.005 [1.000; 1.009] *	
Age > 65years			7.953 [7.256; 8.649]***
NIHSS > 6			3.740 [2.882; 4.598]**
Fibrinogen > 400mg/dL			2.988 [2.290; 3.686]**
McFadden R	0.416	0.378	0.310
AUC	0.780	0.759	0.897
AIC	204.435	217.741	240.376
BIC	253.636	245.565	268.200
Deviance	186.435	207.741	230.376
Num. obs	1749	1929	1929
***p < 0.001; **p < 0.01; *p < 0.05			

After variable selection (forward stepwise algorithm), age, sex, NIHSS and fibrinogen remained in the model 2. We finally dichotomized variables in model 2 according to their AUC. These cutoffs corresponded to: age > 65y, NIHSS > 6, and fibrinogen > 400mg/dL. Including these dichotomized variables showed the best discrimination capacity of stroke (AUC = 0.897) (Table 2, model 3). This model was correctly calibrated according to the Hosmer-Lemeshow test and Brier score (*p-value* = 0.013). However, calibration plots showed a good calibration for ischemic stroke in probabilities higher than 98% whereas for MA prediction calibration was good for a predicted probability lower than 10% (Additional files 1 and 2). Predicted probability for ischemic stroke in a man, older than 65 years, with initial NIHSS

higher than 6 and fibrinogen > 400mg/dL would be 99%. However, the opposite case (woman, younger than 65, NIHSS < 6 and fibrinogen < 400mg/dL) would still have 75% probability of being a stroke.

Clinical and radiological findings in MA

Specific review of MA cases found that only 50% had a previous diagnosis of migraine (32.4% without aura and 17.6% with aura) although up to 79.4% of them fulfilled diagnostic criteria of migraine at the time of code stroke. Only 47% had a family history of migraine.

The most predominant symptom was sensory disturbance (73.5%), especially negative symptoms (80.0% of all sensory disturbances), followed by motor (64.7%), language (35.3%), visual (26.5%) (of which 55.6% were positive and 44.4% were negative symptoms), and vertigo (5.9%) (Fig. 2). Up to 76.47% of MA patients presented with more than one symptom at a time. Onset of symptoms was sudden in 12 patients (35.3%) and 11 patients (32.4%) did not experience headache during admission. Five patients (14.7%) persisted with symptoms at discharge (sensory fluctuant symptoms) and at follow-up.

The first neuroimaging performed in these patients was NCCT + CTA in 17 (50.0%), NCCT + CTA + CTP in 12 (35.3%) and a plain NCCT in 5 (14.7%). Two patients showed abnormal perfusion (16.7% of patients with CTP). One case was a 36 years old female patient with history of migraine with visual aura, who presented with acute onset of left-hand weakness and numbness associated with dizziness without headache, initial NIHSS was 1. CT perfusion showed asymmetry between hemispheres in flux and volume maps, with an increased flow in the territory of the right middle cerebral artery, thalamus and bilateral occipital cortex at 38 minutes of symptom onset. The second case was a 49 years old male patient with migraine with visual aura, who started with visual aura followed by headache and language disturbances in form of motor aphasia. CT perfusion showed hypoperfusion of the left occipital area with a reduction of T_{max} with preserved CBVol at 63 minutes of symptom onset. In both cases onset to neuroimaging was earlier compared with cases without perfusional alterations, mean time 50 min (SD 17.67) compared to 199.2 min (SD 138.6) (Fig. 3).

Discussion

MA is a well-known stroke simulator. Our study showed that one out of every 100 code stroke activations evaluated by a trained vascular neurologist was a MA mistaken for a stroke and was treated with fibrinolysis in the same rate. Age, sex, NIHSS, and fibrinogen levels were the most differential characteristics between MA and ischemic strokes but a diagnostic tool using these variables was not useful for clinical practice. Moreover, after reviewing MA cases we did not find a clinical or radiological pattern that could be tested to improve prediction.

Door-to-needle time has progressively diminished over the last years, provoking a faster decision-making, and consequently a higher prevalence of stroke mimics (including MA) treated with fibrinolysis [7, 10–

12]. For this reason, diagnostic predictive models to discriminate between these two entities would allow a quick assessment at the emergency department, reducing misdiagnosis and, consequently, avoiding non-indicated treatments.

We have observed a prevalence of MA that reaches 1.1% of all code strokes after the first assessment by a vascular neurologist. These numbers are almost identical than the previously reported [1]. However, the real prevalence of MA in the code stroke in our population is probably higher since the proportion of stroke mimics activated by the emergency services is around 20% and drops to 7% after the evaluation by a vascular neurologist [7].

To our knowledge, this is the first study comparing initial characteristics between MA and ischemic stroke codes. Almost 30% of MA were treated with rTPA in a very similar rate than strokes, pointing out the difficulty of distinguishing both diseases at the first evaluation. Younger age and female sex were the most predictive variables associated with MA. Other variables that showed an acceptable discriminatory capacity were NIHSS and fibrinogen levels, which were lower in MA. Although multivariate model with cut-off points showed a good calibration and discrimination capacity, the probability to predict MA was very low, probably due to the low number of MA cases in the cohort. Given the best-case scenario (woman, age $\leq$ 65, NIHSS $\leq$ 6, fibrinogen $\leq$ 400mg/dL), the maximum probability of being a migraine was 25% and therefore the model could not be useful in the clinical practice to rule out ischemic stroke and avoid unnecessary treatments.

Although age is a crucial factor and MA prevalence is higher between 15–49 years [13, 14], half of MA cases in our study were 50 to 75 years old, denoting that MA can happen at any age [15]. In addition, stroke in young people is not infrequent and MA patients carry a higher risk of ischemic stroke [16]. Therefore, although age is very different between the two groups it cannot help to rule out any differential diagnosis. Female sex was two times more frequent in MA as is the prevalence of this disease in the general population [13].

Initial severity measured by NIHSS was lower in MA and accordingly code stroke was more frequently activated in primary care centers than in the street or home where severe cases are usually evaluated. We did not find significant differences in the vital signs or blood test findings at arrival except a lower level of fibrinogen in the MA compared with ischemic strokes. This result agrees with previous studies, which found that high fibrinogen levels were associated with higher risk of cardiovascular diseases (including stroke) [17] and a poorer functional outcome from acute ischemic stroke [18]. Further studies would be required to assess the utility of fibrinogen as a biomarker to distinguish MA from stroke. A recent study has shown that CGRP salivary levels are increased in migraine patients compared to controls, especially in ictal phase [19]. Future studies could analyze the utility of this or other migraine biomarkers to rule out stroke mimics in code stroke.

Finally, we described the main clinical and radiological findings of MA in order to generate new hypothesis for future studies. However, we didn’t find any characteristic that could be exclusive of MA. Only half of the patients fulfilled IHS criteria previous to admission. Like in previous studies [5, 20], we

found a higher prevalence of sensory symptoms, mainly negative like numbness, making it hard to distinguish from a thalamic stroke. Although visual aura is the most frequent in MA [4], it is not the most common in cases that raise stroke suspicion. Therefore, although some presentations can be more suggestive of a migraine etiology (positive sensory/visual symptoms, progressive onset, presence of a headache), atypical presentations of MA are frequent and patients and professionals should be aware. In the neuroimaging study two patients had abnormal (increased or decreased) perfusion imaging in the initial CT study performed in the first 60 minutes after symptom onset. Previous case reports and small studies have shown hypoperfusion during the first 120 minutes [21, 22] and hyperperfusion even at 3–6 days [23–26] with high variability between studies. A recent study found 3 patients (12%) with perfusion-CT alterations among 25 cases of MA attended after code stroke activation (two of them with an increased mean transit time (MTT), and one with increased MTT and reduced cerebral blood flow) [5]. Therefore, CT-perfusion seems not useful to rule out ischemic stroke except in a small proportion of patients. MRI with diffusion-weighted imaging (DWI) would be the ideal neuroimaging study to definitely rule out an ischemic stroke but it is not widely used in the code stroke because of time and price costs [27, 28].

Our study has some limitations. The number of MA was low and this could have prevented us from finding other significant associations and obtaining a good model calibration. The proportion of MA was low since code stroke was evaluated by a vascular neurologist. Nevertheless, this is the biggest study of MA in this type of setting. Blood test data were missing in a relative high proportion of patients probably because some test could not be completed to avoid time delays. However, there were no differences between patients with and without missing data. And finally, only a third of MA were studied with CT perfusion and this may have not allowed us to find more radiological findings.

Conclusions

MA is a frequent cause of mimic in the code stroke with one third of patients receiving unnecessary fibrinolytic treatment. A predictive model including age > 65, male sex, NIHSS > 6 and fibrinogen > 400 mg/dL showed a good discrimination capacity to distinguish between MA and ischemic stroke, but a low calibration performance. Future studies should involve migraine biomarkers in order to improve clinical decision making.

Abbreviations

AUC
Area under the curve
CBF
Cerebral blood flow
CBV
Cerebral blood volume
CRP

C reactive protein
CTA
CT angiography
CTP
CT perfusion
DBP
Diastolic blood pressure
DWI
diffusion-weighted imaging
ED
Emergency department
MA
Migraine with aura
mRS
modified Rankin scale
MTT
Mean transit time
NCCT
Non-contrast brain CT
NIHSS
National institute of health stroke scale
ODT
Onset to door time
ONT
Onset to needle time
SBP
Systolic blood pressure
TIA
Transient ischemic attack.

Declarations

Ethics approval and consent to participate

Cases were not formally involved in the study design or the outcome measures. The study protocol was approved by the Ethical Review Board of Parc de Salut Mar, Barcelona, Spain. All patients signed an informed consent form to be included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AMG and ECG were involved in the conception and design of the study, interpretation of data, and in the writing of the manuscript. AMG and ASP contributed to data acquisition. ECG, AO and JJB performed the statistical analysis. All authors interpreted the data, reviewed the manuscript, and approved the final version.

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Figures

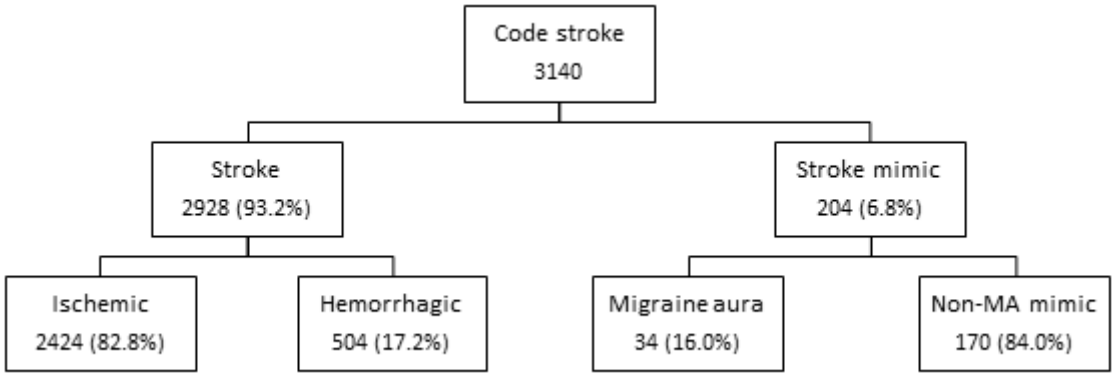

Figure 1

Flowchart illustrating the different groups included in this study.

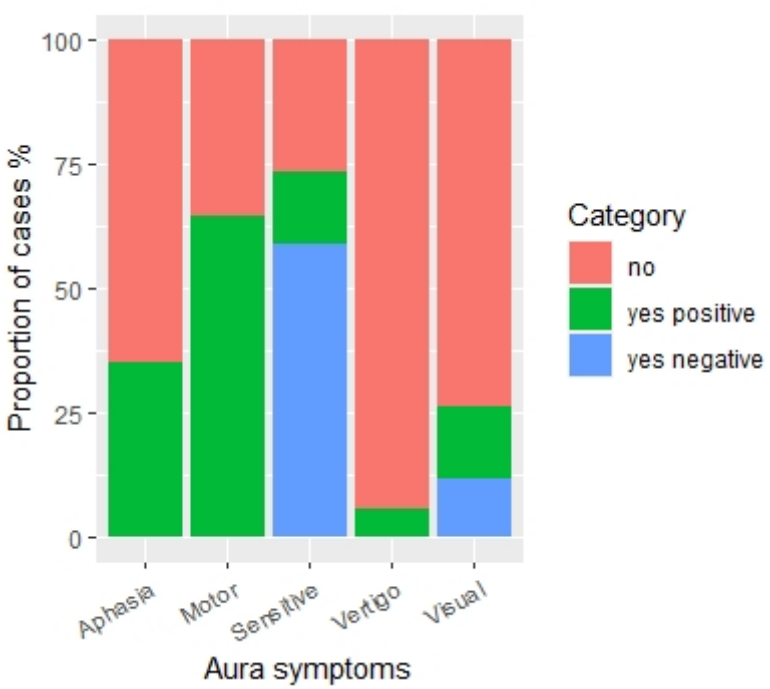

Figure 2

Bar chart representing type of symptoms observed in patients with MA attended in code stroke.

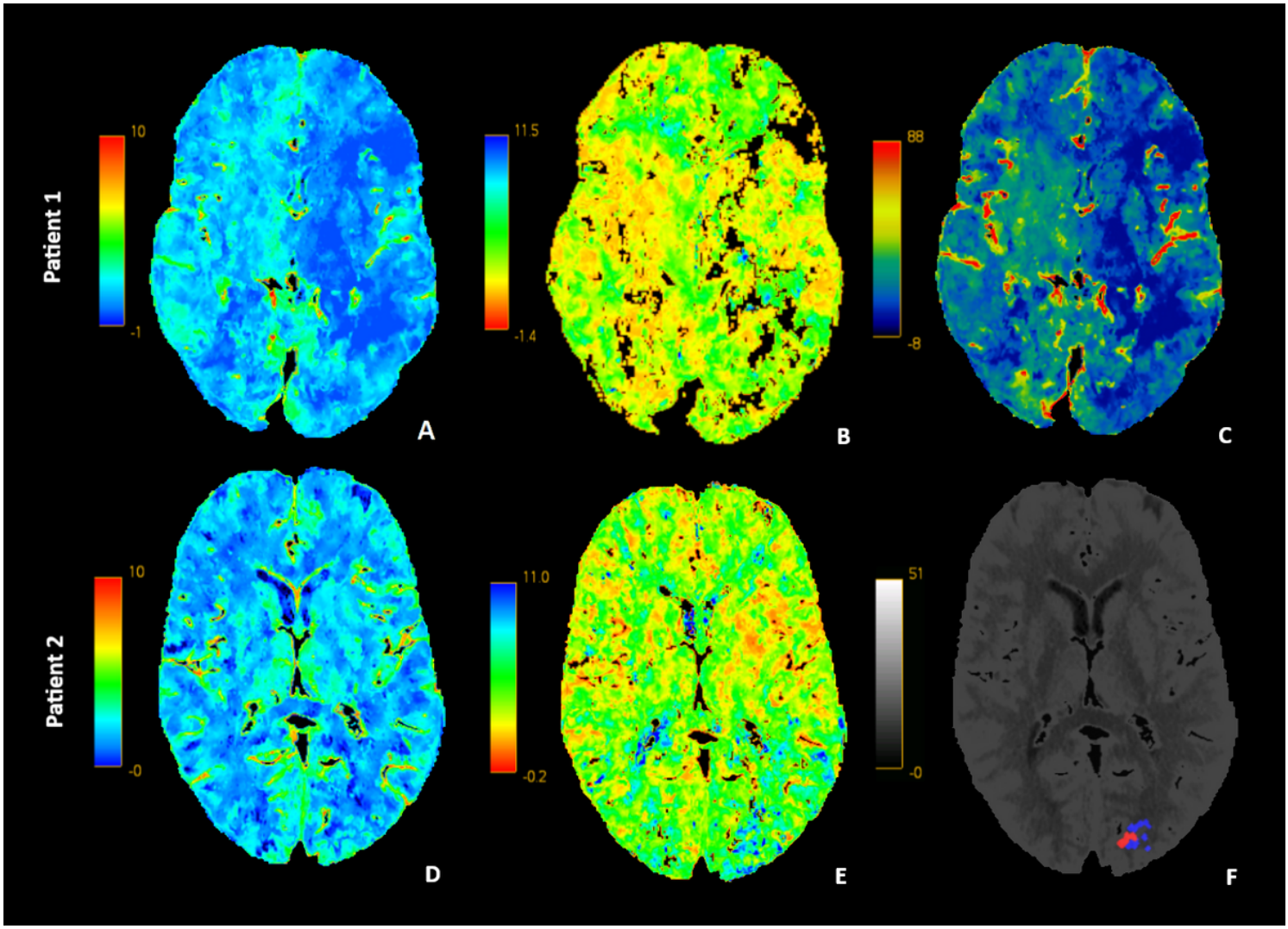

Figure 3

Perfusion-CT maps showing perfusional alterations in two patients. Images A (volume CBV), B (Tmax) and C (Flow CBF) from patient 1 show hyperperfusion (asymmetry between hemispheres in flux and volume maps, showing hyperflow in the territory of right cerebral middle artery, thalamus and bilateral occipital cortex). Images D (volume CBV), E (Tmax) and F (CBV/Tmax mismatch) from patient 2 show hypoperfusion of the left occipital area with increased Tmax and preserved CBVol.

Supplementary Files

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