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Challenges in Diagnosis of Ischaemic Stroke: A Descriptive Study of Stroke Mimics and Missed Strokes

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Abstract

Background: Despite technologic advances, stroke remains a difficult clinical diagnosis. We aimed to investigate the rate and characteristics of stroke mimics (SM) and missed strokes (MS).

Research Methodology: We used data of consecutive "suspected stroke" admissions in a tertiary academic Hospital from January 2016 to July 2018. Diagnosis of SM was based on the absence of an ischaemic infarct on neuroimaging plus the presence an alternate discharge diagnosis. MS were defined as any patient with a discharge diagnosis of stroke whose stroke-like symptoms were missed in the Emergency Department (ED).

Findings: Of 1745 patients reviewed, 63% were ischaemic stroke, 18% Intra-Cranial Haemorrhage (ICH), and 18% SM. We detected 95 MS. Stroke risk factors were significantly less common among SM and MS compared to stroke patients. Younger age, female gender, dizziness, ataxia, absence of limb weakness, and absence of certain vascular risk factors were predictors of SM. For MS, the predicting factors were young age (<55), confusion at presentation, hypercholesterolemia, and absence of hypertension.

Conclusion: Atypical presenting symptoms can cause over and under-diagnosis of stroke. MS and SM are similar in many aspects. These diagnostic errors occur more often in younger patients with less severe neurological symptoms and symptoms attributable to posterior circulation.

Keywords: Stroke; Stroke mimic; Missed stroke; Diagnostic errors

Abbreviations: SM: Stroke Mimics, MS: Missed Strokes, ED: Emergency Department, ICH: Intra-Cranial Haemorrhage, IS: Ischaemic Stroke, DWI: Diffusion-Weighted Imaging, NCCT: Non-Contrast CT Scans, OR: Odds Ratios, NIHSS: National Institute of Health Stroke Scale, AF: Atrial Fibrillation, DM: Diabetes Mellitus, IHD: Ischaemic Heart Disease.

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Introduction

Generally, 40,000 to 80,000 preventable deaths occur each year in the United States due to misdiagnosis [1]. Based on different studies, between 9 to 19% of all cerebrovascular accidents are missed in emergency departments [2-4]. A missed stroke diagnosis can prevent patients from receiving adequate therapy, leading to preventable mortality, morbidity, and costs [5].

On the other hand, over-diagnosis of stroke in ED occurs prevalently, especially when targeting a shorter door to needle time for thrombolysis [6], when a detailed neurological examination and history taking is skipped in order to save time for subsequent better outcome of hyperacute therapy [7]. Although multiple studies have confirmed the safety of thrombolysis in stroke mimics [8-11], the substantial financial burden of unnecessary treatment, testing, and hospital care are still significant issues [12].

In the present study, we aimed to investigate the most common diagnostic errors in detecting stroke by defining the rate and characteristics of stroke mimics (SM) and missed strokes (MS).

Research Methodology

This is a retrospective cross-sectional study. We retrospectively analyzed stroke registry data of consecutive ischaemic stroke (IS) admissions and all patients discharged with the final diagnosis of stroke from a tertiary teaching hospital in Sydney, Australia from January 2016 to July 2018. The study was approved by the local human research and ethic committee.

In order to find SM, we reviewed all admissions to the stroke units. Those patients who were admitted to the stroke unit and were discharged with a diagnosis other than stroke were categorized as "potential SM". Final Diagnosis of SM was based on the absence of ischaemic infarct on Diffusion-Weighted Imaging (DWI) MRI or three consecutive non-contrast CT scans (NCCT) plus the presence of an alternative discharge diagnosis.

To detect MS, we assumed all patients who were discharged with a diagnosis of stroke but were not initially admitted to the stroke unit as "potential MS". We identified MS among these patients as those whose stroke-like symptoms were missed in ED.

A stroke research fellow reviewed the electronic medical records of the patients. Data including age, gender, presenting symptoms, admission National Institute of Health Stroke Scale (NIHSS), length of stay in stroke bed, and cerebrovascular risk factors.

We categorized the presenting problems as: motor symptoms, sensory symptoms, vertiginous symptoms, speech disturbance, confusion, loss of consciousness, unilateral facial weakness, ataxia, visual disturbance, falls, amnesia, headache, dysphagia and non-neurological symptoms. We compared SM and MS characteristics with each other and with IS.

Statistical analysis

Continuous variables were analyzed using the Student t-test and The Mann-Whitney U-test was used to measure differences in outcomes with skewed distributions and ordinal variables. Differences in categorical variables were assessed using the Fisher's Exact Test. Stepwise backward logistic regression was performed to identify independent predictors of SM and MS and odds ratios (OR) with 95% CI. The outcome was the final diagnosis of SM/MS or ischaemic stroke and predictor variables were dichotomized. A value of P<0.05 was considered significant. All analyses were conducted using IBM SPSS Statistics v.24.

Results

We analyzed 1,745 patients with suspected stroke from which 1,108 (63%) were IS, 321(18%) were ICH and 316 (18%) were SM. We identified 95 MS. Eighty-nine percent (288) of SM had a negative MRI for stroke in addition to non-stroke discharge diagnosis. The diagnosis of mimic in the rest of the cases was based on the absence of infarction in multiple NCCT plus the presence of an alternative diagnosis.

Table 1 shows the demographics of SM and MS compared with IS patients. The median age of SM was 69 years which was significantly lower than IS (P< 0.0001). Twenty-two percent of SM were younger than 55 years versus 8% of stroke patients (P <0.0001). Similarly, MS were significantly younger than stroke patients (P <0.0001). There was no significant difference in median age between SM and MS nor when comparing the proportion of patients younger than 55 years. Although the majority of MS were women (55%), there was no meaningful difference according to gender between the three groups. Median NIHSS was considerably lower in SM (1, IQR) and MS (2, IQR) compared to stroke patients (4 IQR), (P <0.0001). MS had a lower median NIHSS than SM (P <0.0001). Thirty-nine percent of SM and 66% of MS had an initial NIHSS of zero. Length of stay in stroke bed was significantly shorter for the SM group (2 days for SM *vs*. 4 for strokes, P <0.0001).

Table 2 illustrates the distribution of major cerebrovascular risk factors among SM, MS and stroke patients. Stroke risk factors were significantly less common among SM in contrast to stroke patients except for HTN and previous stroke which were comparable in both groups. Hypertension and hypercholesterolemia were the most common risk factors among all patients. AF and ischaemic heart disease were notably more prevalent among stroke patients while hypercholesterolemia was more common in the SM and MS groups. Generally, MS had more risk factors than SM.

In terms of presenting problems, dizziness, confessional state, loss of consciousness, and visual disturbance were more frequent among both SM and MS whereas lateralized weakness was more common in strokes **(Table 3)**. No meaningful difference indicated in the prevalence of unilateral sensory loss and speech

Table 1 Demographic characteristics.

Variables	IS	SM	MS	IS *vs*. SM	IS *vs*. MS	SM *vs*. MS
	n=1108	n=316	n=95			
Age, median (range)	77 (22-101)	69 (22-97)	71 (19-96)	<0.0001	<0.0001	0.794
Age < 55, n (%)	91 (8%)	69 (22%)	18 (19%)	<0.0001	0.01	0.668
Gender, male (%)	616 (56%)	165 (52%)	43 (45%)	0.305	0.054	0.244
LOS, days mean (STD)	8.6 (9.1)	3.8 (4.6)	4.7 (11.4)	<0.0001	<0.0001	0.45
LOS Stroke Bed, mean (STD)	5.0 (5.8)	2.9 (3.4)	1.1 (5.7)	<0.0001	<0.0001	0.005
NIHSS Admission, Median (IQR)	4 (1-10)	1 (0-3)	0 (0-1)	<0.0001	<0.0001	<0.0001
IS: Ischaemic Stroke, SM: Stroke Mimics, MS: Missed Strokes, LOS: Length of Stay in the Hospital						

Table 2 Presenting symptoms.

Presenting symptoms	IS	SM	MS	IS *vs.* SM	IS *vs.* MS	SM *vs.* MS
	n=1108	n=316	n=95			
Limb weakness	441 (41%)	51 (15%)	29 (30%)	<0.0001	0.08	0.003
Sensory loss	93 (8%)	28 (9%)	10 (10%)	0.819	0.446	0.686
Dizziness	68 (6%)	78 (25%)	9 (10%)	<0.0001	0.192	0.001
Speech disturbance	154 (14%)	55 (17%)	18 (20%)	0.126	0.172	0.76
Confusion	47 (4%)	23 (7%)	10 (10%)	0.038	0.011	0.29
Loss of consciousness	99 (9%)	14 (4%)	3 (3%)	0.009	0.054	0.772
Facial droop	46 (4%)	10 (2%)	1 (1%)	0.513	0.171	0.469
Ataxia	17 (2%)	18 (6%)	1 (1%)	<0.0001	1	0.09
Visual disturbance	45 (4%)	21 (9%)	6 (6%)	0.067	0.285	1
Falls	26 (2%)	9 (3%)	2 (2%)	0.68	1	0.341
Amnesia	2 (0%)	5 (2%)	0 (0%)	0.007	1	0.595
Headache	44 (4%)	4 (1%)	1 (1%)	0.02	0.253	1
Dysphagia	3 (0%)	0 (0%)	1 (1%)	1	0.281	0.233
Non-neurological	21 (2%)	0 (0%)	4 (4%)	0.007	0.128	0.003
IS: Ischaemic Stroke, SM: Stroke Mimics, MS: Missed Strokes						

Table 3 Vascular risk factors.

Risk factors	IS	SM	MS	IS *vs.* SM	IS *vs.* MS	SM *vs.* MS
	n=1198	n=316	n=95			
Hypertension	706 (64%)	203 (64%)	48 (51%)	0.895	0.015	0.022
Atrial Fibrillation	346 (31%)	45 (14%)	18 (19%)	<0.0001	0.014	0.26
Diabetes	248 (22%)	53 (17%)	20 (21%)	0.035	0.898	0.359
Hypercholesterolaemia	434 (39%)	163 (52%)	77 (81%)	<0.0001	<0.0001	<0.0001
Previous stroke	222 (20%)	71 (22%)	10 (11%)	0.345	0.021	0.012
Ischaemic heart disease	267 (24%)	41 (13%)	7 (7%)	<0.0001	<0.0001	0.149
Smoking (current)	98 (9%)	11 (4%)	9 (9%)	0.001	0.851	0.027
IS: Ischaemic Stroke, SM: Stroke Mimics, MS: Missed Strokes						

difficulty between the three groups. MS presented more often with unilateral weakness than SM, whereas SM presented more commonly with dizziness than MS.

Logistic regression revealed, age younger than 55, low NIHSS score, dizziness, confusion, ataxia, amnesia, absence of limb weakness, and absence of certain vascular risk factors including Atrial Fibrillation (AF), Diabetes Meletus (DM), hyperlipidaemia, and Ischaemic Heart Disease (IHD) were predictors of SM **(Table 4)**.

For MS, the predicting factors were young age (<55), low initial NIHSS, confusion at presentation, hypercholesterolemia, and absence of hypertension and IHD **(Table 5)**.

Table 4 Logistic regression model for predicting stroke mimics.

Variables	OR	95% CI
Age at onset under 55	3.84	(2.52-5.84)
NIHSS < 8	5.73	(3.36-9.77)
Limb weakness	0.56	(0.37-0.84)
Dizziness	4.57	(2.93-7.12)
Speech disturbance	1.78	(1.16-2.73)
Confusion	2.67	(1.45-4.92)
Ataxia	4.37	(2.02-9.45)
Amnesia	14.38	(2.44-84.75)
Headache	0.24	(0.08-0.72)
Atrial Fibrillation	0.43	(0.29-0.63)
Diabetes	0.62	(0.42-0.92)
Hypercholesterolaemia	2.65	(1.94-3.62)
Ischaemic heart disease	0.63	(0.42-0.96)
Smoking	0.39	(0.17-0.65)
NIHSS: National Institute of Health Stroke Scale		

Discussion

Of all potential stroke admissions in a tertiary hospital in Sydney, 18% were discharged as SM. The prevalence of SM among stroke patients ranges from 1.8 to 31% according to different studies. Such a wide range is due to different inclusion criteria used in those studies. Our data indicated that SM was younger with lower initial NIHSS and less vascular risk factors. These are in accordance with other studies [6,9,11,13]. There was no significant difference according to gender among SM in our study, but several other studies revealed a female predominance in SM [6,8,14].

Ninety-five MS were included in our study. MS comprises 1.1% of IS patients and 0.5% of all stroke patients in our study. The final diagnosis of stroke was asserted by neuroimaging studies along with clinical characteristics. Other studies used different criteria

Table 5 Logistic regression model for predicting Missed Strokes.

Variables	OR	95% CI
Age at onset under 55	2.55	(1.28-5.11)
NIHSS < 8	16.68	(5.17-53.85)
Confusion	4.12	(1.70-10.01)
Hypertension	0.37	(0.22-0.62)
Hypercholesterolaemia	10.71	(5.89-19.48)
Ischaemic heart disease	0.24	(0.11-0.54)
NIHSS: National Institute of Health Stroke Scale		

to capture MS. Compared to stroke patients, MS were younger with lower admission NIHSS. Although females were dominant among MS (55%), there was no meaningful difference according to the gender between MS and stroke patients. These results accord with previous studies [15-18].

According to our results, age younger than 55, female gender, low NIHSS score, dizziness, ataxia, absence of limb motor symptoms, and absence of certain vascular risk factors including AF, DM, HPL, and IHD were predictors of SM. Cognitive impairment, loss of consciousness (LOC), confusion, and non-neurologic symptoms were predictors of SM in Hand et al. study [19], while global aphasia without unilateral weakness was the main predictor of SM in Zinkstok et al. and Winkler et al. studies [8,20]. Among non-neurological symptoms, chest pain was more frequently seen in SM as opposed to stroke patients in one study [21]. Nine percent of SM in our study presented with non-neurologic symptoms from which vomiting and chest pain, were most common.

Similar to SM, vascular risk factors were generally less common in MS compared to stroke patients. However, the rate of hypercholesterolemia was exceptionally higher in MS. Interestingly 81% of MS had hypercholesterolemia. This contrasts with another study which revealed less lipid-lowering medication use in MS as an independent risk factor for MS [22].

Unilateral limb weakness, speech difficulty, confusional state, and unilateral sensory disturbance were the most frequent presenting symptom among MS. Compared to stroke patients, MS more often presented with confusion, dizziness, and visual disturbance and less often with lateralized weakness and unilateral facial weakness. Dizziness and confusional state were independent risk factors for MS. Arch et al. found dizziness, vomiting, syncope and seizure at the onset were associated with MS [20,21], whereas confusion, LOC and the concomitant presence of neurologic and psychiatric conditions were predictors of MS in Richoz et al. study [22].

Conclusion

To our knowledge, this is the first study investigating the characteristics of SM and MS together. Our data revealed that SM and MS patients share a number of key features. In general, these patients are younger, they present with less severe symptoms according to their initial NIHSS and their length of stay in hospital is shorter as opposed to ischaemic stroke patients. Additionally, stroke risk factors are less common in these two groups and their presenting symptoms are different from stroke patients.s

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