Stroke mimics: Clinical characteristics and outcome

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ABSTRACT

الأهداف: معرفة مدى انتشار مشابهات السكتة الدماغية (Stroke mimics) وطبيعة المرض لدى المرضى السعوديين المحولين إلى قسم الطوارئ في مدينة الملك عبدالعزيز الطبية – الرياض، عند حدوث أعراض عصبية مفاجئة تؤدي للاشتباه بالسكتة الدماغية.

المنهجية: قام الباحثون بمراجعة ملفات المرضى الإلكترونية المشتبه تشخيصهم بالسكتة الدماغية، من شهر فبراير 2016 إلى شهر يوليو 2018 في مدينة الملك عبدالعزيز الطبية – الرياض. وفي ضوء ذلك تمت مقارنة نتائج مشابهات السكتة الدماغية بالسكتة الدماغية الحقيقية، ودراسة العوامل المؤدية لحدوثها باستخدام تحليل الانحدار اللوجستي. وبناءً على ذلك تم قبول هذه الدراسة من قبل مجلس المراجعة المؤسسية في مركز الملك عبدالله العالمي للأبحاث الطبية.

النتائج: أجريت هذه الدراسة على عينة من المرضى السعوديين قوامها (1,063) مريض في مدينة الملك عبدالعزيز الطبية – الرياض. وأشارت نتائج الدراسة إلى أن (131) أي (12.3%) مريض تم تشخيصهم بمشابهات السكتة الدماغية. كما بينت الدراسة أن أكثر المسببات لمشابهات السكتة الدماغية كانت على النحو الآتي: اضطرابات التوازن الدهليزي (peripheral vestibular disorder) بنسبة (27.4%) والاضطرابات النفسية (psychogenic) بنسبة (24.4%). إضافةً إلى ذلك أظهرت نتائج الدراسة أن معدل حدوث مشابهات السكتة الدماغية لدى البالغين والنساء أكثر، وفي ذات السياق أوضحت الدراسة أن أمراض الضغط والسكري والتدخين أقل لدى المصابين بمشابهات السكتة الدماغية. وفي ضوء ذلك كشفت الدراسة أن المصابين بمشابهات السكتة الدماغية بعد انتهاء المدة العلاجية في المستشفى يصبحون قادرين على الحركة من غير مساعدة، بالإضافة إلى قلة احتمالية حصول مضاعفات كما أن فترة التنويم تكون لديهم أقل. ومن زاوية أخرى توصلت الدراسة إلى أن عوامل التنبؤ بمشابهات السكتة الدماغية تشمل العمر، الجنس (أنثى)، عجز خفيف عند الوصول للطوارئ وأن يكون بحالة صحية قبل حدوث الأعراض.

الخلاصة: خلّصت هذه الدراسة إلى أن مشابهات السكتة الدماغية شائعة لدى المرضى المشتبه إصابتهم بالسكتة الدماغية. يتطلّب من الأطباء الأخذ بالحسبان لمشابهات السكتة الدماغية خصوصًا في أول ٦ ساعات من حدوث الأعراض.

Objectives: To study the prevalence and nature of stroke mimics (SM) among Saudi patients who came to the emergency department with a sudden neurological deficit and suspected stroke.

Methods: The electronic health records from February 2016 to July 2018 of patients who were admitted to the Stroke Unit at King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia (KAMC-RD) with a suspected stroke were all reviewed. A comparison between SM and stroke was established. Our study identified the predictors of SM by using logistic regression analysis. This study was approved by the local institutional review board.

Results: Out of 1,063 patients, 131 (12.3%) had SM. The most common causes were a peripheral vestibular disorder (27.4%) followed by psychogenic causes (24.4%). Stroke mimics were more common among younger individuals and women. Arterial hypertension, diabetes, and smoking were less likely to be found in SMs. At discharge, individuals with SM were more likely to be independent, had milder deficits, and shorter hospital stays. Predictors of SM were young age, female gender, mild deficit at presentation, and good functional status before the stroke.

Conclusion: The incidence of stroke mimics is common among suspected stroke patients. Practicing physicians should consider potential diagnostic errors, particularly in the hyperacute phase of the stroke.

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Stroke is one of the most common leading causes of mortality worldwide.[1] Annually, the diagnosis of stroke in about 25 million people. Moreover, 6.5 million people die from stroke each year.[2] Stroke is a life-threatening condition and requires immediate assessment so that patients can receive time-critical interventions such as tissue plasminogen activator (tPA). Therefore, accurate diagnosis is crucial. Sudden onset of neurological symptoms, or signs localized to brain arterial territories, are cause for suspicion of stroke. In most of these cases, a clinical assessment supported by brain computed tomography (CT) and basic laboratory tests are typically enough to make an accurate diagnosis in an emergency department. However, the misdiagnosis of stroke is relatively common. Stroke mimics (SM) are defined as acute onset of focal neurological symptoms, which later diagnosed with a non-vascular origin.[3] In some patients with SM may erroneously receive intravenous thrombolysis therapy.[4,5]

Stroke mimics are common in patients with suspected stroke.[3-7] Conditions that mimic stroke include metabolic disorders such as hypoglycemia, hyperglycemia, hypernatremia, hyponatremia, uremia, metabolic encephalopathy, and hyperthyroidism.[4,6,7,8] Moreover, migraine, seizure, psychological disorders, demyelinating diseases, and brain tumors may also mimic stroke.[4,6-8] The characteristics and statistics about SMs among suspected cases of stroke in Saudi Arabia have not been reported. Yahia et al. reported that 15.9% of patients with suspected stroke were SMs, psychiatric etiology was the commonest.[9] In this study, we estimated the prevalence, types, and predictors of SM among Saudi patients.

Methods.

Study design, area, and settings. The electronic health records from February 2016 to July 2018 of patients who were admitted to the Stroke Unit at King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia (KAMC-RD) with a suspected stroke were all reviewed. Neurological examination, routine labs, and imaging studies were done for suspected stroke or transient ischemic attack (TIA) patients. Finding occlusions in the Computed Tomography (CT) image does not confirm the diagnosis of a stroke. We defined stroke mimics when all the patients met the following criteria: (1) sudden neurological deficit resembling stroke within the 24 hours before the arrival at the emergency department. (2) The initial clinical impression by an emergency physician, basic laboratory tests, and brain CT imaging were not sufficient to make a definite diagnosis. (3) Required the expertise of a vascular neurologist to exclude stroke and TIA. (4) MRI of the brain did not reveal acute cerebral infarct.

Our inclusion criteria included all patients who prestneted to the emergency department with sudden neurological defecits from February 2016 – July 2018 at KAMC-RD. Moreover, the exclusion criteria included any patients with a final diagnosis of ischemic stroke, hemorrhagic stroke, TIA, and cerebral sinus thrombosis.

Data collection. This study variables were collected from electronic health records, which are demographics, vascular risk factors, final diagnosis, length of stay (LOS), admission and discharge 1) modified Rankin scale (mRS) and 2) National Institute of Health Stroke Scale (NIHSS), and in-hospital death. Vascular neurologists determined a final diagnosis (ischemic stroke, hemorrhagic stroke, TIA, cerebral sinus thrombosis, or SM).

Table 1 - Baseline characteristics for stroke mimic patients in comparison to stroke.

Characteristics	Mimics (N=131)	Strokes (N=932)	*P*-value
Mean age±SD (years)	51±15	60±12	<0.000*1*
Female sex n(%)	70 (53.4)	309 (33.1)	<0.000*1*
Medical history n(%)			
Ischemic heart disease	11 (8.5)	112 (12.4)	0.20
Arterial hypertension	56 (43.1)	645 (71.6)	<0.0001
Diabetes mellitus	60 (45.8)	564 (62.6)	0.0005
Dyslipidemia	37 (28.5)	270 (29.9)	0.7
Body Mass Index (Mean±SD)	30±6	29±6	0.06
History of smoking	11 (8.5)	153 (17.0)	0.01
Previous ischemic stroke/TIA†	39 (30.0)	238 (26.4)	0.4
Median (IQR) time from onset to arrival — Min	660 (2760)	540 (1500)	0.2
mRS 0 — 1 before stroke n(%)*	106 (85.5)	806 (88.4)	0.4
Median (IQR) NIHSS score at admission**	2 (4)	5 (8)	<0.0001
Treatment with tPA n(%)	3 (2.3)	76 (8.2)	0.01
Neurological symptoms n(%)			
Speech and language	29 (22.3)	369 (41.4)	<0.0001
Motor weakness	62 (47.7)	554 (62.2)	0.7
Sensory symptoms	41 (31.5)	267 (29.9)	1.0
Gait imbalance	24 (18.5)	231 (25.9)	0.08

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Table 2 - Causes of stroke mimics (N=131).

Mimic	n (%)
Peripheral vestibular disorder	36 (27.4)
Psychogenic	32 (24.4)
Unspecified	14 (10.6)
Seizure	12 (9.2)
Migraine	12 (9.2)
Metabolic/drugs	12 (9.2)
Musculoskeletal	4 (3.1)
Space occupying lesion	4 (3.1)
Peripheral vascular disease	2 (1.5)
Demyelination	2 (1.5)
Syncope	1 (0.8)

Table 3 - Outcome of stroke mimics compared to strokes.

Outcome	Mimics (N=131)	Strokes (N=932)	*P*-value
In-hospital mortality	3 (2.3)	27 (2.9)	1.0
Dependency at discharge*	17 (15.7)	339 (39.8)	<0.0001
Length of stay, median (IQR)	2 (2)	5 (11)	<0.0001

NIHSS - national Institutes of health stroke scale, IQR - interquartile range, *Defined as modified Rankin scale >2, **Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 (normal function) to 42 (death), with higher scores indicating a greater deficit

Table 4 - Predictors of mimics among suspected strokes (multivariate logistic regression analysis).

Independent variable	Odds ratio	95%CI for OR		*P*-value
		Lower	Upper	
Age	0.9	0.95	0.98	0.0006
Female gender	1.62	1.02	2.58	0.04
Medical history:				
Ischemic heart disease	1.04	0.50	2.17	0.9
Arterial hypertension	0.37	0.23	0.61	< 0.0001
Diabetes mellitus	0.99	0.60	1.65	0.9
Dyslipidemia	1.34	0.82	2.19	0.2
Body Mass Index	1.00	0.97	1.03	0.8
History of smoking	0.49	0.23	1.04	0.06
NIHSS score at admission	0.81	0.75	0.87	< 0.0001
modified Rankin Scale (mRS) before stroke <2	3.15	1.65	6.00	0.0005
Sudden neurological symptoms:				
Speech and language	0.77	0.46	1.27	0.3
Motor weakness	0.94	0.60	1.50	0.8
Sensory symptoms	1.23	0.76	2.01	0.3
Gait imbalance	0.73	0.43	1.26	0.2

CI - confidence interval, NIHSS score - National Institutes of Health Stroke Scale scores range from 0 (normal function) to 42 (death)

Data analysis. We have made a cohort comparison between SM and real stroke patients. We compared the In-hospital death, dependency at discharge (mRS>2), and LOS between the 2 groups. Continuous variables data were represented as the mean±(SD). Categorical variables were expressed as percentages. We used the student's t-test and χ^2 test to compare means and proportions, respectively. We examined potential predictors of SM among all patients with suspected stroke using multivariate logistic regression analysis. The model included age, gender, vascular risk factors, NIHSS at admission, and type of neurological symptoms. Stata statistical program (version 15) was used for the statistical analysis.

Results. Among 1,063 patients admitted with suspected stroke, 131 (12.3%) patients had SM. Three patients only with SMs received tPA therapy. The baseline characteristics for stroke mimic patients in comparison to stroke are presented in **Table 1**. Patients with SM were younger (51 vs. 60 years of age; $p<0.0001$) and were more likely to be women (53.4 % of patients with SM were women vs. 31.1% of real stroke patients; $p<0.0001$). Moreover, vascular risk factors tend to be less in SM patients. Arterial hypertension found only in 43.1% of patients with SM vs. 71.6% of patients with stroke, $p<0.0001$. Diabetes found only in 45.8% of patients with SM vs. 62.6% of patients with stroke, $p=0.0005$. Also, 8.5% of patients with SM were active smokers vs. 17.0% of patients with stroke, $p=0.01$. Stroke mimics were less likely to present with speech and language symptoms (22.3% of patients with SM vs 41.4% of patients with stroke, $p<0.0001$), and were associated with a milder deficit (median NIHSS 2 vs 5 for patients with SM versus patients with stroke, respectively, $p<0.0001$).

The most common causes of SM were peripheral vestibular disorder (27.4%), psychogenic (24.4%), seizure (9.2%), migraine (9.2%), and metabolic and drugs (9.2%). **Table 2** shows the causes of SM in our cohort. No significant difference in mortality between the SM and stroke groups (2.3% vs. 2.9 %, $p=1.0$). **Table 3**. Represented the outcomes of SM and real strokes, SM had a lower rate of dependency at discharge than patients with stroke (15.7% vs 39.8%, respectively, $p<0.0001$), and shorter LOS (median LOS 2 vs. 11; $p<0.0001$). Predictors of SM is shown in **Table 4**. Predictors are younger age (odds ratio [OR] 0.9, 95% confidence interval [CI], 0.95-0.98; $p=0.0006$), female gender (OR 1.6, 95% CI 1.02-2.58; $p=0.04$), no history of hypertension (OR 0.37, 95% CI 0.23-0.61; $p<0.0001$), stroke severity (NIHSS score) (OR 0.81,

95% CI 0.75-0.87; $p<0.0001$), and functional status (mRS) before stroke (OR 3.15, 95% CI 1.65-6.0; $p=0.0005$).

Discussion. The study indicates that 12.3% of our cohort wrongly diagnosed with a stroke. In previous studies, the prevalence of SM among potential strokes ranged from 1.5% to 44%.[7,10-14] This wide range reflected a lack of consistent diagnostic criteria, study inclusion criteria, study setting (community versus hospital-based studies), site of care (emergency department, stroke unit, TIA clinic, general practice), expertise involved in establishing the diagnosis, and confirmatory tests. Our estimate for the diagnosis of SM was relatively lower than that in many other studies.[15] This may have been due to strict inclusion criteria, which included an evaluation by a specialized stroke neurologist and confirmation using brain MRI to make a diagnosis. We may have underestimated the prevalence of SM because many patients were diagnosed with SM during the initial assessment by emergency physicians and were not referred to stroke neurologists, which resulted in exclusion from the study. Likewise, results from previous studies, 2.3% of patients with SM in our study were treated with tPA.[3-5] The SITS International Stroke Thrombolysis Register Results showed that among 10,436 patients treated with tPA for acute stroke, 429 (4.1%) were cases of SM. The risk of an intracerebral hemorrhage resulting from tPA treatment was lower in patients with SM than that in patients with stroke.[4] None of the three patients treated with tPA in our cohort had any complications. Furthermore, we showed that younger age, female gender, milder deficits, lack of history of hypertension, and no disability before suspected stroke were factors that differentiated SM from a stroke. Several studies have reported similar findings.[16-20] Other studies reported other distinguishing factors that predicted SM like systolic blood pressure ≤140 mmHg, diabetes, no history of arrhythmia, altered level of consciousness, and normal ocular movements.[21,22] The brain attack study showed that SM could be predicted by changes in higher mental functions, clinical signs in other systems, ability to determine exact time of symptoms onset, unequivocal focal neurological symptoms or signs, and presence of lateralizing signs.[7] In our study, neurological symptoms did not differ between SM and real strokes, except that speech and language impairment was less common in patients with SM. However, symptoms did not predict SM in our logistic regression analysis. This study lacked neurological signs evaluation because of its retrospective nature.

Stroke mimics are a heterogeneous group of disorders. The top 5 types in our study were a peripheral vestibular disorder, psychogenic, seizure, migraine, and metabolic and drugs. These common causes, among many others, have been reported previously.[4-22] Gibson et al[15] conducted a systematic review of 29 studies that included 8,839 patients, 25% were diagnosed with SM. The five most frequent SM in this analysis were seizure, syncope, sepsis, migraine, and brain tumors.[15] The SITS International Stroke Thrombolysis Register date showed that the most common types of SM were functional (30.8%), migraine (17.5%), and seizure (14.2%).[4] In contrast to many other studies, peripheral vestibular disorder was the leading cause of SM in our cohort. For example, Gibson et al[15] reported vertigo as the cause of SM in only 3.2% of patients. Selection bias may have played a role in the results of our study. Moreover, the diagnosis of posterior circulation stroke or TIA in patients with pure vertigo or dizziness requires an exceptional skill. Many physicians may lack these skills and may not feel confident enough to exclude stroke, which may result in a lower threshold for seeking consultation, resulting in admission and further investigation.

Our study had some limitations. First, the study cannot be generalized because of the setting. Second, it was a hospital stroke unit-based review, which may not reflect the true prevalence of SM in other areas such as communities, emergency departments, and TIA clinics. Third, retrospective studies are susceptible to bias. Fourth, the loss of follow-up interrupts the confirmation of diagnoses. We depended solely on the opinion of the treating stroke neurologist on discharge, with confirmation using MRI results. Posterior circulation TIA is a diagnostic challenge when patients arrived at an emergency department with resolved neurological signs and symptoms, and negative brain MRI. Magnetic resonance imaging diffusion-weighted images may miss 15-20% of posterior fossa infarctions, especially in the first 48 hours of the onset of symptoms.[23,24] Some cases of strokes may be missed despite evaluation by stroke neurologists and the acquisition of MRI images.

In conclusion, SMs are common among patients with suspected stroke, and these patients may be subjected to unnecessary investigations, harmful intervention, and high-risk medications. Stroke mimics occur in young patients and women and may occur in patients with fewer risk factors for stroke. The SM patients typically present with mild neurological deficits and may be erroneously treated with tPA. Importantly, stroke mimics takes time and effort to diagnose, which create a burden on different departments. Actively,

practicing physicians work to identify patients with SM early in the diagnostic process. Prospective, nation-wide studies are highly needed to characterize this subgroup of patients further.

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