Cohort Study of Features Used by Experts to Diagnose Transient Ischemic Attack

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Abstract

Background and Purpose: The diagnosis of transient ischemic attack (TIA) is largely dependent on a process of clinical decision-making that remains poorly characterized in the absence of a validated and accessible biomarker or imaging test. We performed a retrospective chart review to identify variables associated with a final neurologist diagnosis of TIA/stroke. **Methods:** Records for all patients seen in The Ottawa Hospital's Stroke Prevention Clinic in 2015 were analyzed for patient and referral characteristics, features of the presenting neurological event, and final diagnosis by a stroke neurologist (classified as definite, possible, or definite not TIA/stroke). Multinomial logistic regression analysis with backward elimination was used to identify variables associated with the final diagnosis. **Results:** Our inclusion criteria were met by 1894 patients. After backward elimination, 23 potentially important variables were identified, including monocular vision loss (odds ratio [OR]: 30.4, 95% confidence interval [CI]: 14.6-63.3), symptoms of sudden onset (OR: 28.3, 95% CI: 14.2-56.2), unilateral weakness affecting 2 or 3 of face, arm, or leg (OR: 17.7, 95% CI: 9.8-31.7), and homonymous hemianopia (OR: 16.6, 95% CI: 8.1-34.0). **Conclusions:** Accurate diagnosis of TIA is essential to initiating appropriate secondary stroke prevention therapies. A focus on elements of the patient history most commonly associated with a final diagnosis of TIA/stroke may help to identify patients in greatest need of urgent SPC assessment and allow for the provision of effective and efficient stroke prevention services.

Keywords

stroke, stroke prevention, transient ischemic attack, decision analysis, stroke and cerebrovascular disease

Introduction

The diagnosis of transient ischemic attack (TIA) is challenging and has substantial implications for patients. Failure to diagnose TIA can be detrimental to patients as it leaves them at higher risk of subsequent stroke, but overdiagnosis can be problematic as well. Patients incorrectly labeled as having had a TIA are subject to numerous unnecessary tests and their true underlying condition may fail to be addressed.¹ Furthermore, assessment of these patients contributes to the wait times in stroke prevention clinics (SPCs) and may impede the assessment of true high-risk patients with TIA.

While the utility of magnetic resonance imaging (MRI) is widely discussed in relation to the diagnosis of TIA, it is not readily available for many patients. Only 24% of stroke centers in Canada have access to MRI within 48 hours,² and access is even more limited in many other regions around the world. Moreover, two-thirds of patients with symptoms

consistent with TIA do not have a visible lesion on imaging, so both normal and abnormal computed tomography (CT) and MRI are compatible with a clinical diagnosis of TIA.³

In North America and throughout much of the world, patients referred to SPCs with suspected TIA have their final diagnosis determined by an expert (usually a neurologist or geriatrician), often one with stroke-specific training. Therefore, clinical decision-making by expert physicians remains the de facto gold standard for the diagnosis of TIA, yet it is a

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standard that is poorly described.⁴ Even best practice guidelines provide little direction on which clinical features are supportive of a diagnosis of TIA.⁵ For all these reasons, we sought to characterize the clinical features that are essential to TIA.

We previously performed a systematic review of the available literature to identify the factors that neurologists identify as important to their diagnosis of TIA versus TIA mimic.⁶ That review suggested that the type of deficit (especially weakness and speech impairment), mode of onset (sudden), and lack of stereotyped episodes were core elements of the neurologist's diagnosis of TIA. Based on this review, we sought to model the real-world clinical decision-making of neurologists working in an SPC in a Canadian comprehensive stroke center using a retrospective chart review of patients' clinical histories and final diagnoses.

Methods

Study Design

A retrospective chart review was performed using data from the charts of all patients referred to The Ottawa Hospital's SPC in 2015. The Ottawa Hospital's SPC accepts referrals from general practitioners, emergency department physicians, and medical specialists from Ottawa and surrounding areas within the Champlain region. The catchment area includes 1.2 million people across Eastern Ontario and the number of SPC patient visits is approximately 2000 per year. In 2015, 8 different neurologists—including 4 with stroke subspecialty training—assessed consultations after initial triage by nurse specialists. Patients were triaged based on the initial history and any completed investigations; a CT scan and vascular imaging (carotid Doppler or CT angiogram) were always completed prior to the visit, with expedited echocardiogram and Holter monitor.

Patients referred with a provisional diagnosis of TIA/stroke were eligible for inclusion. Patients were excluded if they did not complete a visit with the SPC, either due to subsequent admission or due to lack of presentation at the appointment. Patients were also excluded if they did not experience an index clinical event, for example, if they were referred for management of an incidental stroke identified on imaging or of asymptomatic carotid stenosis. The study was approved by the Ottawa Health Sciences Network Research Ethics Board.

Information collected from each chart included the following: age, sex, ABCD₂ score and its individual components, reason for referral, referral source, imaging findings, patient risk factors, final diagnosis, and specific event characteristics. Based on our systematic review, we extracted the following features of the clinical presentation: event duration, onset, number of events, stereotypy, unilateral motor weakness (face, arm, or leg), unilateral sensory loss, positive sensory symptoms, aphasia, dysarthria, altitudinal field defect, homonymous hemianopia or complete vision loss, diplopia,

positive visual phenomena, ataxia/unsteadiness, vertigo/spinning/movement, dizziness not otherwise specified, lightheadedness, loss of consciousness/syncope/presyncope, pain, headache, chest pain, involuntary movement/jerking, confusion, amnesia, and situational/positional onset.

Two authors (T.F., C.Q.W.) independently extracted pilot data from the first 100 charts. Discrepancies between the 2 extractions were identified. This revealed which variables were ambiguously defined, leading to differing interpretations of the same data. Variables were redefined after consensus discussion, and the data collection template was modified accordingly. Using the final template, one author extracted data from the charts of all included patients. To confirm validity of data extraction, post hoc duplicate review of 200 charts was performed independently by separate authors (T.F., S.G., M.S.). Where discrepancies were found, they were adjudicated by consensus discussion of all authors.

Statistical Analysis

Descriptive statistics (mean and standard deviation or frequency and percentage) were used to describe patient and referral characteristics, features of the presenting neurological event, and final diagnosis (classified as definite, possible, or definite not TIA/stroke). Because the dependent variable was nominal with 3 levels, we used multinomial logistic regression analysis with a generalized logit link function to identify variables associated with the final diagnosis. All candidate variables were entered into the initial model and backward elimination was used with the significance level for staying in the model set at $\alpha = .15$. We chose a higher level of significance to avoid excluding potentially important variables. Pairwise odds ratios (ORs) and their 95% confidence intervals were produced comparing the different levels of the dependent variable (definite stroke/TIA vs may be; definite not vs may be, definite stroke/TIA vs definite not). The goodness of fit of the model was assessed using deviance and Pearson χ^2 statistics. Because the prevalence of missing data was low, we excluded patients with missing values on any covariates. In case of missing data on the original blood pressure recording in the emergency department, we substituted the first recorded blood pressure for the emergency blood pressure in the calculation of the ABCD₂ score. This method was selected as it has been used in other similar published analyses.⁷ Statistical analysis was performed using Statistical Analysis Software (SAS, version 9.4).

Results

Two thousand two hundred eighty-one patients were referred to The Ottawa Hospital's SPC in 2015. Of these, 1894 (83%) met eligibility criteria and were included in our study. Baseline demographics, stroke risk factors, ABCD₂ score, and imaging characteristics of all patients included in the analysis are displayed in Table 1.

Table 1. Baseline Demographics, Stroke Risk Factors, ABCD₂ Score, and Imaging Characteristics of Included Patients.

Variable	All Patients (N = 1894)
Age, mean (SD)	67 (14)
Gender, n (%)	
Male	947 (50%)
Female	947 (50%)
Referral source, n (%)	
Emergency physician	1070 (57%)
General practitioner	543 (29%)
Specialist	281 (15%)
Stroke risk factors, n (%)	
Hypertension	1065 (56%)
Dyslipidemia	844 (45%)
Diabetes	384 (20%)
Coronary artery disease	289 (15%)
Peripheral vascular disease	68 (4%)
Atrial fibrillation	184 (10%)
Smoking	274 (14%)
Prior TIA/stroke	268 (14%)
ABCD ₂ score, n (%)	
0-4	1540 (81%)
5-7	354 (19%)
Imaging characteristics, n (%)	
Acute/subacute infarct	150 (8%)
Possible symptomatic carotid stenosis	275 (15%)

Abbreviations: SD, standard deviation; TIA, transient ischemic attack.

Neurologists diagnosed 705 patients with definite TIA/stroke (37%), 397 with possible TIA/stroke (21%), and 792 with definite not TIA/stroke (ie, TIA mimic; 42%). Non-TIA/stroke diagnoses are compiled in Table 2. Patients referred by specialists were more likely to receive a final diagnosis of TIA (46%) than those referred from emergency departments (38%) or general practitioners (30%).

Of 31 candidate variables entered into the initial multinomial logistic regression mode, the final model identified 23 explanatory variables that remained after backward elimination (significance level to stay $\alpha = .15$). A total of 119 (6.3%) observations were dropped due to missing values for at least one explanatory variable among those that remained in the final model (1775 observations were used). Because the prevalence of missing data was low, patients with missing values on any covariates in the multinomial logistic regression were dropped.

We were most interested in the comparison between patients diagnosed with definite TIA/stroke and those diagnosed with TIA mimic (classified as “definite not TIA/stroke”), and for that reason, we present pairwise ORs for those comparisons only. The remaining comparisons and the full multivariable logistic regression model after backward elimination are presented in Table e-1. Event characteristics, demographics, and imaging features significantly associated with a diagnosis of definite TIA/stroke versus TIA mimic are summarized in Table 3.

Definite TIA/stroke was significantly more likely if symptoms were of sudden onset versus gradual onset (OR: 28.3) or

Table 2. Non-TIA/stroke Final Diagnoses.

Mimic	Number	Percent of Total Mimics
Unspecified (it was stated that the final diagnosis was not stroke/TIA but otherwise not specified)	254	32.07%
Migraine (or possible migraine or migraine variant)	134	16.92%
Syncope/presyncope (due to orthostatic hypotension, vasovagal syncope, or unspecified)	76	9.60%
Peripheral vestibulopathy	39	4.92%
Psychiatric (anxiety/stress/other psychiatric diagnosis)	36	4.55%
Cranial nerve palsy	30	3.79%
Peripheral neuropathy/radiculopathy	30	3.79%
Seizure/epilepsy	28	3.54%
Transient global amnesia	22	2.78%
Cardiac, arrhythmias, hypertensive crises	17	2.15%
Delirium/dementia/other neurodegenerative/neurocognitive disorders	16	2.02%
Other medical condition (not primarily neurological, ie, viral illness)	16	2.02%
Primary ocular pathology	12	1.52%
Substance induced (alcohol, recreational drugs, prescription medications)	12	1.52%
Musculoskeletal pathology	11	1.39%
Other neurological diagnoses	10	1.26%
Asymptomatic carotid stenosis (patient still presented with symptoms but not attributable to stenosis and ultimately not diagnosed as TIA/stroke)	9	1.14%
Secondary stroke (had a prior stroke, now returning with symptoms that are not diagnosed as another stroke or TIA by the neurologist)	9	1.14%
Global cerebral hypoperfusion	6	0.76%
Myopathy/neuromuscular junction disease	5	0.63%
Demyelinating disease	5	0.63%
Intracranial bleed/amyloid angiography	5	0.63%
Movement disorder	4	0.51%
Carotid dissection	3	0.38%
Giant cell arteritis	3	0.38%

Abbreviation: TIA, transient ischemic attack.

sudden onset versus unknown onset (OR: 3.7). Symptom duration of at least 1 minute versus less than 1 minute was also significantly associated with a diagnosis definite TIA/stroke (OR: 5.6). Patients with vision loss in the form of amaurosis fugax (OR: 30.4) or homonymous hemianopia (OR: 16.6) were more likely to be diagnosed with definite TIA. Unilateral weakness affecting one area (face, arm, or leg) was significantly associated with a diagnosis of TIA/stroke (OR: 4.5), but the association was even greater for weakness involving more than one body region (2 or 3 of face, arm, or leg; OR: 17.7). Isolated ataxia, vertigo, and diplopia were not independently associated with the final diagnosis of TIA, but the odds of

Table 3. Model of Features Associated With Definite TIA/Stroke Versus Definite Not TIA/Stroke.^a

Clinical Features	OR (95% CI)	P Value
Subacute or acute imaging findings	47.4 (19.2-117.2)	<.0001
Monocular vision loss (amaurosis fugax)	30.4 (14.6-63.3)	<.0001
Sudden vs gradual onset	28.3 (14.2-56.2)	<.0001
Unilateral weakness of 2 or more regions (face/arm/leg)	17.7 (9.8-31.7)	<.0001
Homonymous hemianopia	16.6 (8.1-34.0)	<.0001
Aphasia	7.1 (4.5-11.1)	<.0001
Any 2 of 3 of vertigo/ataxia/diplopia	6.1 (2.4-15.8)	.0002
Duration ≥ 1 minute vs < 1 minute	5.6 (3.0-10.2)	<.0001
Dysarthria	4.6 (2.8-7.6)	<.0001
Unilateral weakness (any of face/arm/leg)	4.5 (2.9-7.0)	<.0001
Sudden vs unknown onset	3.7 (2.6-5.2)	<.0001
Age ≥ 60	2.7 (1.9-3.8)	<.0001
Smoking	2.6 (1.7-4.0)	<.0001
Ipsilateral carotid stenosis (>50%)	2.4 (1.5-3.7)	.0001
Unilateral sensory loss	1.9 (1.3-2.8)	.0008
Headache	0.60 (0.37-0.94)	.0265
Stereotyped events	0.46 (0.24-0.88)	.0194
2 or more events in the last month	0.44 (0.21-0.92)	.0295
Pain	0.28 (0.13-0.61)	.0013
Positive visual symptoms	0.16 (0.07-0.35)	<.0001
Situational	0.16 (0.04-0.63)	.0085
Lightheadedness	0.15 (0.06-0.36)	<.0001
Jerking	0.13 (0.03-0.48)	.0022
Amnesia	0.11 (0.04-0.35)	.0001
Loss of consciousness	0.05 (0.02-0.15)	<.0001

Abbreviation: CI, confidence interval; OR, odds ratio; TIA, transient ischemic attack.

^aSummary of our multinomial regression analysis. Dependent variables were classified as definite, may be, or definite not TIA/stroke. Remaining comparisons and the full multivariable logistic regression model before backward elimination are presented in Table e-1. Significant *P* value <.05.

definite TIA/stroke were increased in patients with a combination of 2 or 3 of the above symptoms (OR: 6.1). Finally, a diagnosis of TIA/stroke was more likely in patients with dysarthria (OR: 4.6), aphasia (OR: 7.1), or unilateral sensory loss (OR: 1.9). Of these variables, only unilateral sensory loss was no longer significantly associated with a final diagnosis of definite TIA/stroke when compared to possible TIA/stroke. Confidence intervals are presented in Table 3 and did not cross 1 for any of the above variables.

Variables significantly associated with a reduced odds of definite TIA/stroke diagnosis versus TIA mimic are also presented in Table 3. The strongest associations were found with loss of consciousness (OR: 0.05), amnesia (OR: 0.11), involuntary jerking (OR: 0.13), lightheadedness (OR: 0.15), situational onset (OR: 0.16), and positive visual symptoms (OR: 0.16). Other variables significantly associated with a decreased likelihood of definite TIA/stroke included pain, 2 or more events in the last month, stereotyped symptoms, and headache (OR: 0.28-0.60). All of the variables above, except headache and situational onset, were still significantly

Figure 1. Association between ABCD₂ score and final diagnosis of definite transient ischemic attack (TIA)/stroke.

associated with a decreased likelihood of definite TIA/stroke when compared to possible TIA/stroke.

Discussion

Unlike past studies^{8,9} that have looked at rates of agreement or disagreement between emergency department physicians and neurologists' diagnoses of TIA, this study is the first of its kind to model clinical decision-making surrounding TIA diagnosis in vivo. Some of the symptoms we identified are reminiscent of the variables that comprise previously published TIA diagnostic algorithms including the Dawson Score and the Diagnosis of TIA score.^{10,11} However, our study also determined the importance of several features that were not included in these scoring tools, including mode of onset (sudden vs gradual), duration of symptoms, and pattern of events (ie, stereotyped, recurrent, or situational).

In addition to the clinical features of the index event, particular patient characteristics including age and smoking were associated with a diagnosis of TIA/stroke in our model. It is important to note, however, that while demographic factors may inform the pretest probability that a certain patient has had a TIA, they are insufficient to make the diagnosis of TIA. This is the weakness of the frequently cited ABCD₂ risk score, which is heavily weighted toward risk factors at the expense of the specifics of a patient's symptoms. It is perhaps for this reason that the ABCD₂ score shows variability in performance in different patient populations. In our population, only patients with an ABCD₂ score of 5 or more had a greater chance of a final diagnosis of TIA than non-TIA, though this is a more discriminative standard than is often used and applied only to a small number of included patients (354/1894, 19%). Moreover, even at this threshold, ABCD₂ was of moderate predictive value (sensitivity: 35%, specificity: 91%, positive predictive value: 68%, negative predictive value: 70%; Figure 1).

The main limitation of our study is that it is based on the assumption that "expert opinion" in the form of neurologists'

decision-making is the “gold standard” for TIA diagnosis. That being said, in the absence of a reliable biomarker or imaging test, expert opinion is presently the best determinant of TIA diagnosis in clinical practice. In addition, it is standard practice to determine diagnosis through clinician opinions, in most stroke centers in Canada and likely around the world. An additional limitation of our study is that inter-rater reliability could not be assessed since each patient was assessed by only one neurologist. Furthermore, our study was conducted at only one center, and as such it is possible that the results obtained here do not reflect practice generally and are only applicable to our center. We believe this concern may be mitigated by recognizing that the neurologists sampled were trained at a variety of institutions over a number of time periods and brought varied experiences to the process. Lastly, our study is limited by its retrospective approach. Although we were able to demonstrate associations with final diagnosis, conclusions regarding causal relationships cannot be made. In future studies, we hope to further explore TIA diagnosis in a prospective manner, attending to important factors such as patient sex and MRI findings.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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