Incidence and Etiologies of Stroke Mimics After Incident Stroke or Transient Ischemic Attack

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Background and Purpose—Stroke mimics (SM) pose a common clinical challenge, but the burden of SM in patients with previous ischemic stroke (IS) or transient ischemic attack is unknown. The objective of this study was to calculate the incidence of SM in IS survivors, compare it with the incidence of recurrent stroke in the same population, and explore the time-dependent patterns of SM etiologies.

Methods—This prospective cohort study registered SM events and etiologies among 1872 IS and transient ischemic attack survivors diagnosed with index stroke at Haukeland University Hospital stroke unit from 2007 to 2013 by review of medical records. Cumulative incidences of SM were estimated with a competing risks Cox model and compared with incidence of recurrent stroke in the same population.

Results—During 8172 person-years of follow-up, 339 patients had 480 SM events. The cumulative incidence rate of SM during follow-up was 58.7 per 1.000 person-years (95% CI, 53.7–64.2) compared with 34.0 per 1.000 person-years (95% CI, 30.2–38.2) for recurrent stroke in the same time period. The risks of SM and recurrent stroke were highest the first year after index IS or transient ischemic attack. The most frequent SM diagnoses were sequelae of cerebral infarction (19.8%), medical observation, and evaluation for suspected cerebrovascular disease (15.6%) and infections (14.0%). The 2 most frequent and unspecific diagnoses (sequelae of cerebral infarction and medical observation) were clustered in the first months after index stroke.

Conclusions—SM after IS or transient ischemic attack are more frequent than recurrent stroke and the risk is especially high in the early period. SMs are multietiological and unspecific diagnoses are most frequent early after index stroke. **(*Stroke*. 2019;50:2937-2940. DOI: 10.1161/STROKEAHA.119.026573.)**

Key Words: epidemiology ■ incidence ■ ischemic attack, transient ■ stroke

Ischemic stroke survivors have a considerable risk of suffering a recurrent stroke.[1] However, distinguishing strokes from stroke mimics (SM) is often challenging, especially in patients with existing neurological sequelae because of prior stroke and other comorbidities.

SM is usually defined as a condition not resulting from cerebral ischemia that presents with neurological symptoms indistinguishable from stroke.[2] Frequent SMs are infections, migraine, seizures, syncope, vertigo, confusional states, and functional symptoms.[3–6] Although SM have been the subject of numerous studies,[2–5] no studies have assessed frequency and characteristics of SM in patients with prior stroke.

In this hospital-based prospective cohort study, we aimed to calculate the cumulative incidence of SM in patients with prior ischemic stroke (IS) or transient ischemic attack (TIA). Furthermore, we compared the incidence of SM to incidence of recurrent stroke in the same population and explored the time-dependent patterns and etiologies identified as SM.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. All patients >18 years with IS or TIA admitted to the Stroke Unit at the Department of Neurology, Haukeland University Hospital between July 1st, 2007 and December 31st, 2013 were prospectively registered in the Bergen NORSTROKE Registry. New hospital admissions for suspected stroke after initial discharge from the stroke unit and until September 1st, 2016 were identified retrospectively by manual review of complete hospital electronic medical charts from all 10 hospitals in Western Norway. Journals were accessed with a patient-specific national identity number. Patients who moved outside the area covered by our stroke unit during follow-up were excluded. Information on death was gathered electronically from the Norwegian National Registry.

Suspected stroke was defined as a diagnosis of possible stroke in the admission report. Only admissions where diagnostic testing for possible stroke was initiated after initial emergency room evaluation were included in the analysis. The primary *International Classification of Diseases Tenth Revision (ICD-10)* discharge diagnosis was registered. SM was defined as any *ICD-10* discharge

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summary diagnosis other than intraaxial cerebral hemorrhage (I61), ischemic stroke (I63), or TIA (G45, excluding G45.4). The treating physician made the diagnoses.

The definitions and incidence of recurrent IS or TIA for the same follow-up period are previously described for this population.[7]

The study was approved by the Western Regional Ethics Committee with written informed consent obtained from all patients or their representatives.

Statistics

Univariate analyses were performed using the χ^2 test for categorical variables, and Student *t* test or Mann-Whitney *U*-test for continuous variables. Cumulative incidence of SM and recurrent stroke were calculated with the cumulative incidence function after applying the method of Fine and Gray by treating death as a competing risk.[8]

Results

Of 1988 patients diagnosed with IS or TIA during the inclusion period, 116 (5.8%) died during the index admission or were discharged to palliative care. The final cohort consisted of 1872 patients with IS (n=1666) or TIA (n=206).

During a mean follow-up of 5.6 years (median 5.5 years, maximum 9.2 years, 8172 person-years), 339 (18.1%) patients experienced 480 SM events, of which 448 (93.3%) were diagnosed in our stroke unit, 20 (4.2%) in other hospital departments, and 12 (2.5%) in other hospitals. Brain imaging with CT and MRI was done in 426 (88.8%) cases, of which 183 (38.1%) with DWI. Baseline characteristics stratified by SM occurrence are presented in the Table.

The incidence rate of SM during follow-up was 58.7 per 1.000 person-years (95% CI, 53.7–64.2) compared with 34.0 per 1.000 person-years (95% CI, 30.2–38.2) for recurrent IS or TIA.[7] Figure 1 demonstrates cumulative incidence of first SM episode plotted over the cumulative incidence of recurrent IS or TIA. The cumulative incidence of first SM episode was higher than for recurrent stroke at all time points.

The most frequent diagnoses were sequelae of cerebral infarction (I69.3, n=95, 19.8%), medical observation and evaluation for suspected cerebrovascular disease (Z03.3, n=75, 15.6%), infections (N39, J18, J06, A41, n=67, 14.0%), seizures (R56, n=46, 9.6%), dizziness and vertigo (H81, H83, R42, n=40, 8.3%), migraine and other headaches (G43, R51, n=37, 7.7%), and syncope and collapse (I95, R55, n=34, 7.1%). All other diagnoses were registered in 69 cases (14.4%). Figure 2 demonstrates frequencies of the 7 most common diagnoses by time after IS or TIA. Sequelae of cerebral infarction and medical observation and evaluation for suspected cerebrovascular disease were diagnosed most frequently during the first 3 months, with 24 and 18 cases, respectively. The other diagnoses were more evenly distributed in frequency during follow-up.

Discussion

We found that SMs were common after IS or TIA with a higher incidence at all time points compared with recurrent stroke. The cumulative incidence of SM was the highest early after discharge from stroke hospitalization with a gradual decline in new SM cases and stabilized after about 3.5 years during the follow-up period.

Table. Baseline Characteristics at Index Stroke, Stratified by Admissions With Stroke Mimics After Index Discharge (N, %)

	Patients Without SM	Patients With SM	
	n=1533	N=339	*P* Value
Age, y; mean±SD	73.1±13.7	73.7±12.9	0.53
Male sex	857 (55.9)	178 (52.5)	0.26
mRS score at discharge, median (IQR)	2 (1–3)	2 (1–4)	0.83
NIHSS score at discharge, median (IQR)	1 (0–4)	2 (0–4)	0.95
Stroke diagnosis at index admission			0.28
Ischemic stroke	1370 (89.4)	296 (87.3)	
TIA	163 (10.6)	43 (12.7)	
TOAST			
Large-artery atherosclerosis	200 (13.1)	44 (13.0)	0.97
Cardioembolism	492 (32.1)	112 (33.0)	0.74
Small vessel occlusion	174 (11.4)	31 (9.1)	0.24
Other determined cause	27 (1.8)	5 (1.5)	0.71
Undetermined cause	640 (41.8)	148 (43.4)	0.59
Prior ischemic stroke or TIA	293 (19.1)	94 (27.7)	<0.01
Diabetes mellitus	213 (13.9)	68 (20.1)	<0.01
Atrial fibrillation	448 (29.2)	95 (28.0)	0.66
Hypertension	841 (54.9)	211 (62.2)	0.01
Length of stay, median (IQR)	6 (3–10)	6 (3–10)	0.26
Discharge destination			
Home	826 (54.1)	181 (53.6)	0.85
Home with in-home nursing services	146 (9.6)	46 (14.5)	<0.01
Rehabilitation facility	120 (7.9)	32 (9.5)	0.33
Nursing home	377 (24.7)	70 (20.7)	0.12
Other hospital department	57 (3.7)	6 (1.8)	0.07

IQR indicates interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SM, stroke mimics, TIA, transient ischemic attack; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment Classification.

We found a wide array of SM diagnoses after IS or TIA, with some degree of time-dependent clustering for several of the most common diagnoses. In the early period after, the 2 most frequent diagnostic codes (sequelae of cerebral infarction; evaluation for suspected cerebrovascular disease) were unspecific, with no apparent explanation of the new symptoms. Given that the risk of recurrent stroke is also the highest shortly after the index stroke, the balance between recognizing and treating a recurrent stroke and avoiding resource-consuming admissions with SM is challenging.

The most common specific SMs in our study were infection, seizures, dizziness/vertigo, migraine/headaches, and syncope. These conditions are common SM, which may cause stroke-like symptoms directly or by re-expression of old stroke symptoms or poststroke recrudescence.[3,5,9] Infections and

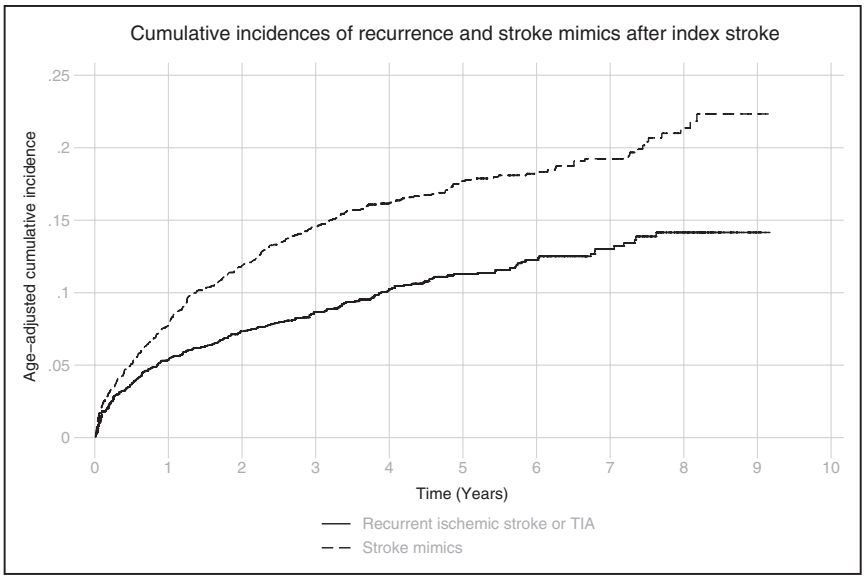

Figure 1. Cumulative incidence function (CIF) of recurrent stroke and stroke mimics after index stroke. TIA indicates transient ischemic attack.

seizures had a peak in frequency after 6 and 12 months, respectively. The other common SM in our study were spread out in frequency over the follow-up period without any clustering.

The etiologies of SM in our study were quite similar as previously described by studies on SM in patients without prior stroke. A meta-analysis listed the 20 most common differential diagnoses of suspected stroke in a total of 813 patients and found that the most common diagnoses were seizures (19.6%), syncope (12.2%), sepsis (9.6%), benign headache disorder (9.0%), brain tumor (8.2%), and functional symptoms (7.4%).[6] Unspecific diagnoses were also common (5%).

Our study has limitations. We may have underestimated the incidence of both SM and recurrent stroke as some patients might have been admitted to other hospitals outside our region, and some SM events might not have been hospitalized. Admission with slight or unspecific symptoms depends on degree of disability and evaluation by the emergency services or the physicians in primary care. The single center hospital-based design raises issues of generalizability. A strength of our study is the manual review of medical records in a large stroke population with thorough evaluation of specific diagnoses for each patient.

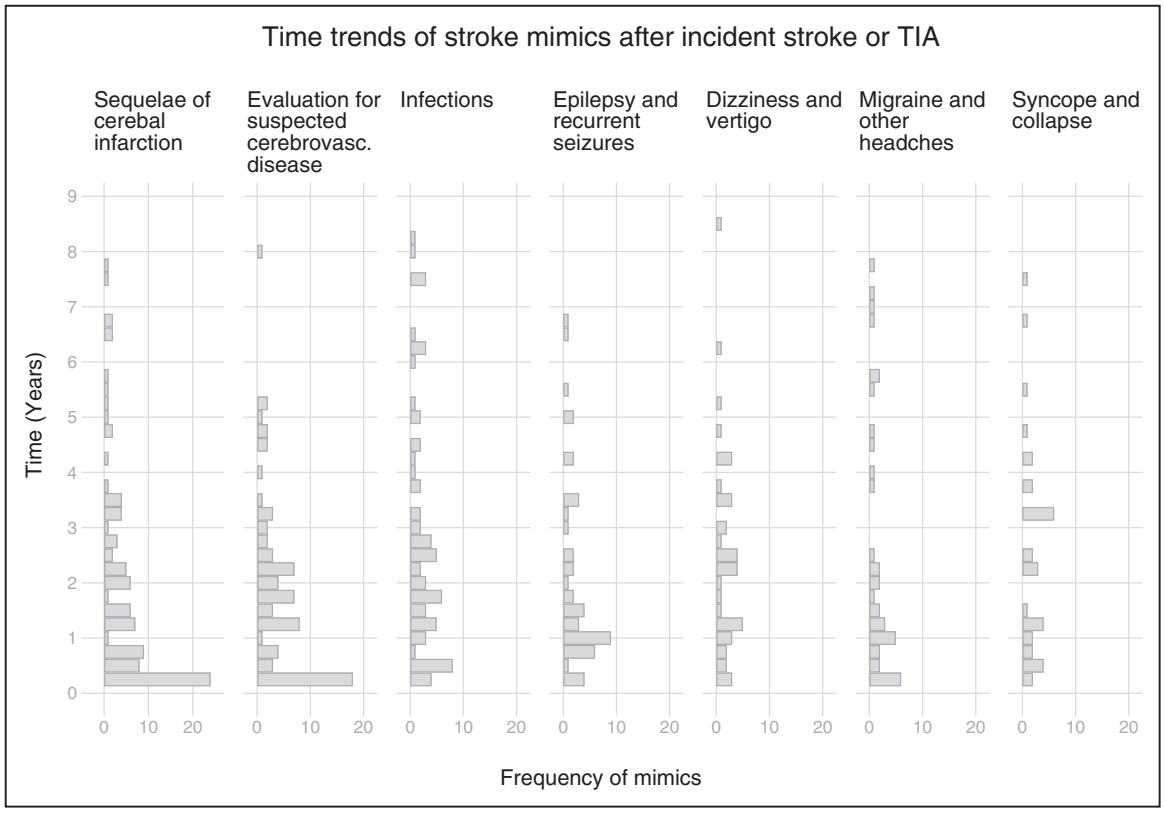

Figure 2. Frequencies of the most common stroke mimics in 3-month clusters after index stroke or TIA (transient ischemic attack).

Conclusions

SM after initial IS are more frequent than recurrent stroke and the risk is especially high right after index stroke. SMs are multietiological in nature and unspecific diagnoses are most frequent directly after index stroke.

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Disclosures

None.

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