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Self-Reported Stroke Symptoms Without a Prior Diagnosis of Stroke or TIA: A Powerful New Risk Factor for Stroke

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Abstract

Background and Purpose—Previously in the REasons for Geographic And Racial Differences in Stroke (REGARDS) cohort, we found 18% of the stroke/TIA-free study population reported ≥ 1 stroke symptom (SS) at baseline. We sought to evaluate the additional impact of these stroke symptoms (SS) on risk for subsequent stroke.

Methods—REGARDS recruited 30,239 U.S. blacks and whites, aged 45+ in 2003–7, who are being followed every 6 months for events. All stroke events are physician-verified; those with prior diagnosed stroke or TIA are excluded from this analysis. At baseline, participants were asked six questions regarding stroke symptoms. Measured stroke risk factors were components of the Framingham Stroke Risk Score (FSRS).

Results—After excluding those with prior stroke or missing data, there were 24,412 participants in this analysis, with a median follow-up of 4.4 years. Participants were 39% black, 55% female, and had median age of 64 years. There were 381 physician-verified stroke events. The FSRS explained 72.0% of stroke risk; individual components explained between 0.2% (LVH) and 5.7% (age + race) of stroke risk. After adjustment for FSRS factors, SS were significantly related to stroke risk: for each SS reported, the risk of stroke increased by 21% per symptom.

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Discussion—Among participants without self-reported stroke or TIA, prior SS are highly predictive of future stroke events. Compared to FSRS factors, the impact of SS on the prediction of future stroke was almost as large as the impact of smoking and hypertension, and larger than the impact of diabetes and heart disease.

Keywords

Acute Stroke; Aphasia; Ischemia; Risk Factors; TIA; Transient Ischemic Attack

Introduction

The increased risk of stroke, myocardial infarction (MI), or vascular death has been well-established among patients who present to medical attention with either a stroke or transient ischemic attack (TIA) [1–3]. However, many of these studies have been among clinical trial participants, which are not necessarily representative of the stroke and TIA patients within a population [4, 5]. Even within population-based studies, the ascertainment methods assume that patients with stroke or TIA seek medical care, either in the inpatient or out-of-hospital setting[3, 6, 7].

It is also well-established that those portions of the population at highest risk for stroke, such as minorities, those with low income or individuals with lower educational levels, or those with co-morbid mental disorders such as depression, have significantly different and lower rates of accessing medical care, even for serious medical conditions[8]. Therefore, there is a high likelihood that the highest risk patients are significantly under-represented in the current stroke risk literature.

Previously, we have reported that 18% of 18,462 participants within the large national cohort of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study without a prior history of diagnosed stroke or TIA responded that they had experienced stroke-like symptoms[9]. These symptoms correlated with the presence of vascular risk factors[9], an increased risk of cognitive impairment[10] and a lower health related quality of life[11], suggesting that these events were likely in part undiagnosed events of cerebrovascular disease, including stroke and TIA. We sought to examine the impact of these self-reported stroke symptoms on the risk of stroke, after adjustment for traditional stroke risk factors.

Methods

Design

The REGARDS study is a national longitudinal cohort study that recruited 30,239 U.S. blacks and whites, aged 45+ in 2003–7, who are followed every 6 months for vascular events and/or death. REGARDS recruited 56% of participants from the Stroke Belt, an area of excess stroke mortality in the Southeastern U.S. that has existed since at least 1940. Approximately 21% of the sample is from the “buckle” of the Stroke Belt (coastal plains of North Carolina, South Carolina, and Georgia); 35% from the remainder of the Stroke Belt (Alabama, Mississippi, Tennessee, Arkansas, Louisiana, and the rest of North Carolina, South Carolina, and Georgia); and the remaining 44% from the other 40 contiguous United States. Approximately 42% of the sample is black and 58% is white, the average age of the cohort at enrollment was 65.3 years. Because the largest stroke-related racial disparities are between blacks and whites,[12] REGARDS only enrolled those reporting race as either non-Hispanic black or white. Within each region, individuals were initially contacted with mailings followed by telephone interview. For those agreeing to participate, telephone interviewers obtained demographic information, medical history, and stroke history by asking “has a health care professional ever told you that you've had a stroke or TIA?”

Trained examiners then visited all participants at their homes to measure blood pressure, height, and weight, obtained an ECG, blood and urine samples, and recorded medications. The examiners were unaware of the participants' stroke/TIA history. Study methods were reviewed and approved by the institutional review boards at collaborating institutions. Additional details of the REGARDS study have been previously published[13, 14].

Stroke Symptoms: Questionnaire for Verifying Stroke-Free Status (QVSFS)

The QVSFS contains eight items. The first two items elicit history of physician-verified stroke, and/or mini-stroke/TIA; a positive response on either of these items excluded people from the current analyses. The remaining six items were asked regarding stroke-like symptoms only if no history of stroke or TIA was reported. Participants were asked about ever having sudden onset of: painless hemi-body weakness, painless hemi-body numbness, loss of vision in one or both eyes, loss of hemi-field vision, or inability to speak or understand. A positive response on ≥1 of these six stroke symptoms indicates a positive stroke symptom history. This scale has been validated in verifying stroke-free status by several authors.[15–18]

Vascular Risk Factors

Traditional vascular risk factors were defined as published in the Framingham Stroke Risk Score (FSRS)[19]. These definitions included: Diabetes—fasting glucose ≥126 mL/dL, non-fasting glucose ≥200 mL/dL, or self-reported use of diabetes medications; systolic blood pressure (SBP) – average of two blood pressures after 5 minutes seated; use of antihypertensive medications – by self-report; atrial fibrillation-history of atrial fibrillation diagnosis or atrial fibrillation on electrocardiogram (ECG); left ventricular hypertrophy-on ECG (LVH); heart disease – self-reported MI, CABG, bypass, angioplasty or stenting, or ECG evidence of MI; current smoking by self-report. More detailed definitions of these variables have been previously published.[20]

Incident Stroke Determination

Incident stroke was determined by adjudication of medical records from suspected stroke events that were self- or proxy- reported on semi-annual telephone contacts. Suspected strokes were considered from hospitalizations and/or physician visits since the last time REGARDS staff spoke with the participant. Reasons for these medical encounters were asked and medical records were sought for stroke, transient ischemic attack (TIA), death, unknown reason for hospitalization, or if the participant was hospitalized for sudden weakness, numbness, trouble speaking, sudden loss of vision, headache, other stroke symptoms. For proxy reported deaths, an interview was conducted with an informed proxy.

Once a potential event was identified, the medical records were retrieved and reviewed by at least two members of the REGARDS Stroke Adjudication Committee; all events were physician-verified. The World Health Organization (WHO) definition of stroke was one of our case criteria for the definition of stroke which is: “rapidly developing clinical signs of focal, at times global, disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin.”[21] We also included events defined as “clinical strokes” which were events not meeting this definition but characterized by symptoms lasting > 24 hours with neuroimaging consistent with acute ischemic or hemorrhage, and consistent with stroke as per the physician adjudicator. For this analysis, we used a combination of WHO-defined or clinical strokes[14].

Analysis

Proportional hazards analysis was employed to assess the association of risk factors (including stroke symptoms) with the risk of stroke. Multiple imputation techniques were employed to reduce potential bias attributable to missing records on suspected stroke outcomes.[22] The focus of the analysis was to assess whether stroke symptoms are an independent risk factor for incident stroke after adjustment for the risk factors included in the FSRS, and to assess the relative contribution of stroke symptoms compared to these traditional risk factors in the prediction of incident stroke events. This was implemented by first fitting a proportional hazards model predicting incident stroke events using the risk factors in the FSRS. The six individual stroke symptoms were considered as predictors added to proportional hazards model after adjustment for the FSRS factors. In addition, the presence of one or more symptoms, as well as the number of symptoms present, were considered as predictors after adjustment for the FSRS factors. To examine improvement in model discrimination, each factor was then removed one at a time, and change in the concordance statistic (c-statistic) between the full model and the model with a predictor variable calculated[23]. We then calculated the integrated discrimination improvement (IDI) using the methods described by Pencina et al to compare risk prediction between models with and without stroke symptoms[24, 25] In layman's terms, the IDI describes how well a new risk factor improves the sensitivity of predicting events without sacrificing specificity, while the C statistic provides a measure for model discrimination.

Results

Follow-up was available on 29,648 (98%) of the 30,239 REGARDS participants. Of these, 2,985 (10%) had prevalent stroke or TIA at baseline, 1,926 (6%) were missing one or more of the Framingham stroke risk factors (primarily glucose level), and 325 (1%) were missing one or more responses for the stroke symptoms were eliminated from the analysis, reducing the analysis cohort to 24,412 participants. There were 381 incident stroke events during a median follow-up of 4.4 years.

Demographics of the participants and vascular risk factor prevalence at baseline are presented in Table 1, stratified by incident stroke status. As expected, participants with incident strokes occurring during the study period were older, more likely to be male and black, and had higher prevalence of vascular risk factors. Participants with a stroke during the study period also had a higher prevalence of stroke symptoms reported during the baseline interview (reported prior to the stroke event itself): 19% vs. 14% for those without stroke. Also presented within Table 1 are the specific stroke-like symptoms reported by participants with and without a subsequent stroke event. The most commonly reported stroke symptom was "sudden painless numbness on one side of the body"; the least common was the "sudden painless loss of vision in part or half of vision".

Table 2 presents the risk of incident stroke associated with the various historical and physiologic measurements from the FSRS. Almost every component of the FSRS was significantly associated with stroke risk, with the exceptions of male sex and current use of anti-hypertensive medication. The largest increased risk for stroke was the category of age, race, and an age-race interaction (younger blacks are at significantly higher risk than elderly blacks when compared to whites), with an overall HR of 2.11.

Table 3 presents the hazard ratios for stroke among participants reporting stroke symptoms compared to those not reporting symptoms. After adjustment for FSRS factors, having one or more of stroke symptoms was significantly related to stroke risk, with the report of any symptom estimated to be associated with a 36% (HR = 1.36; 95% CI: 1.08 – 1.72) increase in risk. The number of stroke symptoms was strongly associated with subsequent stroke risk,

where there was a 21% (HR = 1.21; 95% CI: 1.09 – 1.35) increased risk of stroke for each symptom reported. The most predictive individual symptom was "sudden inability to understand", which was associated with a nearly doubling of future stroke risk (HR = 1.87; 95% CI: 1.27 – 2.75). "Sudden difficulty speaking or communicating" and numbness were also significantly associated with increased risk of stroke. Loss of half vision was associated with a 50% increased risk of subsequent stroke, but the 95% confidence limits barely included 1.0 (0.99 – 2.28) indicating it was not statistically significant.

We also considered measures of model discrimination and reclassification to determine the prognostic significance of including stroke symptoms in the model. The relative change in the integrative discrimination improvement (IDI) after adding the number of stroke symptoms was 3.4%. This was similar to the relative IDI for diabetes (4.4%), atrial fibrillation (3.0%) and LVH (2.3%). In comparison, history of smoking had a much larger relative improvement in IDI (20.1%) as did age, race and the age-race interaction (83.5%). The marginal change in the C statistic was also similar for number of stroke symptoms compared to diabetes, atrial fibrillation and LVH (data not shown).

Discussion

Among participants without a diagnosis of stroke or TIA, one or more self-reported prior stroke-like symptoms was significantly related to the incidence of future stroke events, increasing the risk of a future stroke by 36%. Previously we reported that the presence of stroke-like symptoms were associated with the presence of vascular risk factors [9]. Therefore, we expected that participants reporting stroke symptoms would be at higher risk for stroke. What we did not expect, however, was the strength of the association of stroke symptoms with stroke risk even after controlling for the traditional risk factors. In fact, compared to the traditional Framingham stroke risk factors, the impact of stroke symptoms on the prediction of stroke was almost as large as the impact of hypertension, and larger than the impact of diabetes and heart disease. This is the strongest evidence yet that these stroke symptoms are associated with an increased risk of stroke and may even represent "undiagnosed stroke or TIA". However, these self-reported stroke symptoms may also represent other medical conditions, such as migraine headaches, seizures, syncopal events, dementia, ocular diseases other than vascular occlusion, psychiatric diseases, and others. Therefore, one cannot assume that all of these self-reported events are actually stroke or TIA. Given the large proportion of self-reported stroke symptoms among the population, it is of critical public health importance to further characterize the risk of potentially disabling cerebrovascular events among this group.

Describing stroke risk has been extensively studied in the current literature. One of the best-known examples is the Framingham stroke risk score[19], which is able to describe stroke risk based on simple baseline historical variables, as well as blood pressure and ECG findings. The factors used in the calculation of the FSRS were used in this analysis. While this score is quite valuable and has changed the face of predicting future stroke risk, it should be remembered that the Framingham cohort is largely white and of higher socioeconomic standing than that of the United States population in general, and also represents a cohort willing to come in for routine clinic visits over a several year period. Within the REGARDS cohort, we have shown that stroke-like symptoms are more prevalent among blacks and participants with lower socioeconomic status[9]. This emphasizes the need for varied study populations, including the poor and minority populations, when evaluating stroke risk.

With the exception of vision loss and weakness, a history of each of the individual stroke symptoms was strongly associated with increased risk for subsequent stroke. Given this, it is not surprising that the number of stroke symptoms was the most powerful predictor of

subsequent stroke risk – with the risk increasing 21% for each additional stroke symptom. We have previously reported that 11% of the cohort not reporting stroke/TIA at baseline has a history of exactly one stroke symptom, but 5% have a history of 2 stroke symptoms and this report suggests these individuals would be at a 46% increased risk of subsequent stroke (HR=1.46; $1.21^2 = 1.46$), 1% have a history of 3 stroke symptoms (HR=1.77) and an additional 0.9% have a history of 4 or more (HR =2.14).

A history of problems with understanding or expressing one's self were the two stroke symptoms with the largest increase in stroke risk, increasing risk 1.87 times and 1.75 times respectively. These individual symptoms could be more powerfully associated with stroke risk because they tend to be more reliably reported, or alternatively perhaps because they could indicate a pathology that is more closely associated with stroke risk. We have previously shown that participants were more likely to seek medical treatment for hemi-body weakness than for communication and/or speaking problems[8]. If participants sought care and received a diagnosis of TIA or stroke, they were excluded from this analysis. Therefore, many possible explanations could be hypothesized for the differences seen by specific types of stroke symptoms.

There are several limitations to our analysis. Due to the large volume of participants, the initial baseline interview had to be limited in scope. As a result, the duration, timing, and any associated symptoms with these stroke-like symptom events were not collected. These kinds of clinical data would be helpful in further characterizing these stroke-like events. Another limitation is sample size: while REGARDS is the largest prospective stroke cohort ever collected, at the time of this analysis (after 4.4 years of followup) there were only 381 stroke events. Despite this, we were still able to find quite strong associations in our analysis. Our findings can only be applied to blacks and whites in the U.S., as this study was specifically designed to understand black-white differences. Finally, as is the limitation with any cohort study, the cohort is likely not entirely representative of the population in general, as participants had to have a home address, a telephone, and agree to an in-home visit. However, the strengths of our analysis are that this cohort is truly a nationwide sample without the inherent biases of regional analyses. REGARDS also has the largest number of blacks of any cohort ever assembled in the U.S, and so is well-poised for these kinds of analyses.

In conclusion, stroke-like symptoms as assessed by the 6-item QVSS likely in part represent undiagnosed stroke events, and future studies of stroke risk should query not only prior stroke history but also prior stroke symptoms. Future study of these self-reported stroke-like symptom events are needed to evaluate this high-risk segment of the population.

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Table 1

Demographics, Vascular Risk Factors, and Self-Reported Stroke Symptoms of REGARDS Participants at Baseline Interview

		No Stroke Event Participants (n = 24,031)	Confirmed Stroke Event During Follow-up (n=381)
Demographics and Vascular Risk Factor Prevalence	Age (mean ± SD)	64.3 ± 9.3	70.2 ± 8.7
	Black (%)	39.9	43.3
	Female (%)	55.0	45.1
	Systolic Blood Pressure (mean ± SD)	127.0 ± 16.4	134.7 ± 18.4
	Use of Antihypertensive Medications (%)	48.7	60.4
	Diabetes (%)	20.1	24.9
	Current Smoking (%)	13.8	20.7
	Atrial Fibrillation	7.7	13.9
	Left Ventricular Hypertrophy	5.3	10.5
	History of Heart Disease	20.5	33.6
Self-Reported Stroke-like Symptoms (prior to stroke event, if any)	Any stroke symptom	13.9	18.9
	Number of stroke symptoms	0.27 ± 0.71	0.40 ± 0.94
	Communication problems	3.4	6.3
	Understanding problems	2.5	5.5
	Numbness	8.1	10.8
	Weakness	5.5	6.3
	Vision loss both eyes	4.3	6.3
	Half-field vision loss	2.9	4.5

Table 2

Multivariable Proportional Hazards Model Predicting Stroke Risk Utilizing the "Framingham Stroke Risk Score Factors"

	Parameter	Hazard Ratio (95% CI)
Multivariable Proportional Hazards Model Predicting Stroke risk using the "Framingham Stroke Risk Score Factors"	Age (per decade)	2.11* (1.81 – 2.45)
	Black Race	1.41^ (1.12 – 1.77)
	Age-by-Race Interaction‡	0.74^ (0.60 – 0.91)
	Male sex	1.19 (0.98–1.45)
	Current smoking (vs non-smoking)	2.05* (1.62 – 2.59)
	SBP (per 10 mmHg)	1.14* (1.08 – 1.20)
	Current use of antihypertensive medication	1.16 (0.93 – 1.44)
	Diabetes	1.40^ (1.12 – 1.75)
	Atrial fibrillation	1.43^ (1.08 – 1.89)
	Left ventricular hypertrophy on ECG	1.40 (1.02–1.91)
	Heart Disease history	1.46* (1.18 – 1.81)

‡In our population a significant age by race interaction exists and needs to be controlled for in the models (ie the black participants are at a much higher risk of stroke than white participants at young ages while at older ages the risk is roughly equivalent).

*$p<0.001$,

^$0.001<p<0.05$)

Table 3

Incremental Hazard Ratios and Predictive Value for Self-Reported Stroke Symptoms, after Adjustment for Traditional Framingham Stroke Risk Factors

	Parameter		Hazard Ratio (95% CI)
Incremental hazard and predictive value for adding stroke symptoms one at a time to the model	Any stroke symptom		1.36^ (1.08 – 1.72)
	Number of stroke symptoms (per symptom)		1.21* (1.09 – 1.35)
	Individual Stroke symptoms	Communication	1.75^ (1.20 – 2.55)
		Understanding	1.87^ 1.27 – 2.75)
		Numbness	1.36^ 1.02 – 1.82)
		Weakness	1.32 (0.92 – 1.89)
		Full Vision	1.37 (0.94 – 2.00)
		Half Vision	1.53 (0.95 – 2.45)

* $p<0.001$,

^ $0.001<p<0.05$)