Experience of Stroke Warning Symptoms is Associated with an Adverse Cardiovascular Risk Profile

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Abstract: Population-based studies may provide convincing evidence on whether persons experiencing stroke warning symptoms manifest an adverse cardiovascular risk profile regardless of a history of stroke. Data were analyzed for 9728 US adults aged ≥ 40 years from the National Health and Nutrition Examination Survey1988-1994. Stroke warning symptoms were defined as experiencing one or more of the following for more than 5 minutes: sudden onset of weakness or paralysis of face, arm, or leg; numbness on one side of the face or body; loss of vision in one or both eyes; severe dizziness; or problem with ability to speak or understand. In an analysis excluding those with a history of diagnosed stroke, compared with those who had never experienced stroke symptoms, persons who had experienced symptoms manifested significantly ($P<0.05$) greater prevalence of diabetes, other cardiovascular diseases, and had significantly higher diastolic blood pressure, body mass index, waist circumference, serum triglycerides, ratio of total to high-density lipoprotein (HDL) cholesterol, C-reactive protein, and fibrinogen and significantly lower HDL cholesterol after adjustment for age, sex, and race/ethnicity. Persons who experienced stroke warning symptoms during their lifetime manifested more adverse cardiovascular profiles even though they may not have had a diagnosed stroke. Further risk assessment is recommended for these persons and actions are needed to improve their cardiovascular health.

INTRODUCTION

Stroke remains the third-leading cause of death both in the United States (U.S.) and in the world as a whole [1, 2]. The personal, societal, and economic consequences of stroke are staggering, with an estimated 5,600,000 persons worldwide diagnosed annually with this disorder [3]. Each year in the U.S. about 780,000 people experience a stroke (new or recurrent) and approximately 150,100 die from the event [4]. The lifetime risk of a stroke is approximately 1 in 5 for women and 1 in 6 for men [5]. Between 15% and 30% of stroke survivors become permanently disabled.

Neurological symptoms that are frequently seen before or during a stroke event include a sudden change in speech, visual loss, double vision, numbness or tingling, paralysis or weakness, and non-orthostatic dizziness [6]. Any or all of these stroke warning symptoms (SWS) might be considered a risk factor for future stroke, but these transient and somewhat subjective systoms have unknown associations with the objective characteristics traditionally used to estimate the likelihood of stroke and other cardiovascular diseases.

Not all persons experiencing SWS have a diagnosed stroke, and these symptoms may also indicate other neurological conditions. Indeed, the prior probability of a stroke among patients with neurologically relevant symptoms is only 10% [6]. Some studies indicated that persons experiencing cerebrovascular symptoms may have higher risk of cardiovascular events [7, 8], but the etiologic pathway connecting symptoms to cardiovascular outcome is largely unknown. We used a large population-based health survey among American adults to determine whether the experience of SWS (in the absence of a diagnosed stroke) is associated with the elements of an adverse cardiovascular risk profile.

MATERIALS AND METHODOLOGY

The National Health and Nutrition Examination Survey (NHANES) III was conducted by the National Center for Health Statistics between 1988 and 1994. The survey, which employed a multistage nationwide probability sample of the non-institutionalized US population, included an interview and a detailed clinical evaluation [9].

The current analysis was restricted to NHANES III participants who were aged 40 years and over, participated in the medical examination, and laboratory tests, and were not pregnant at the time of the examination (n = 9728). Information on age, race/ethnicity, smoking status, and the use of antihypertensive, cholesterol-lowering, and diabetes medications was collected during the interview. The average of the last two blood pressure readings taken during the examination was used. Waist circumference was measured by a trained technician to the nearest 0.1 cm in a horizontal plane at the level of the high point of the iliac crest (in the

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mid-axillary line) at minimal respiration. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Definition of stroke warning symptoms (SWS). Responding to a series of explicit, pre-defined questions regarding cardiovascular risk, participants reported whether they had ever experienced any of the following SWS that lasted more than 5 minutes: (1) weakness or paralysis of face, arm, or leg; (2) pronounced numbness, tingling, or loss of sensation on one side of the face or body; (3) a spell of marked loss of vision in one eye or pronounced blurring of vision in both eyes; (4) a spell of severe dizziness; or (5) a spell during which you experienced a problem with your ability to speak or to understand what someone was saying to you. The expected responses for each question were 'yes' or 'no'. The respondents were classified into three categories: those who never experienced SWS (G1), those who had experienced one type (G2), and those who had experienced two or more types of SWS (G3).

Diabetes was defined by report of a physician diagnosis, use of insulin or other diabetic medication, or a concentration of fasting glucose ≥7.0 mmol/l (≥126 mg/dl). History of a stroke was ascertained by self-reported physician diagnosis. Other cardiovascular diseases was ascertained by both self-reported and examination components. Those who self-reported history of physician-diagnosed: a) heart attack or congestive heart failure, b) angina pectoris, or c) intermittent claudication were considered to have other cardiovascular disease. Additionally, those with electrocardiogram (ECG) findings of a) possible or probable myocardial infarction, or b) coronary insufficiency were considered to have other cardiovascular disease.

The lipid accumulation product (LAP) was defined for men as (waist circumference [cm] – 65) x (triglyceride concentration [mmol/l]); it was defined for women as (waist circumference [cm] – 58) x (triglyceride concentration [mmol/l]). These expressions were developed to estimate total-body over-accumulation of lipids. In analyses reported elsewhere LAP performed better than BMI for identifying adults at cardiovascular risk [10, 11].

Besides above measures, we also examined lipid and lipoprotein profiles (serum total cholesterol, HDL and LDL cholesterol, ratio of total to HDL cholesterol, serum triglycerides), glucose metabolism (fasting serum insulin, plasma glucose, percent glycated hemoglobin), blood pressure (systolic, diastolic), medication taking (antihypertensive, cholesterol-lowering), inflammation markers (serum C-reactive protein, plasma fibrinogen), and other cardiovascular risk markers (serum uric acid, creatinine and homocysteine). The details on NHANES laboratory procedures and quality control have been published previously [12].

Statistical Analysis

The skewed variables (LAP, glucose, triglyceride, insulin, uric acid, creatinine, C-reactive protein, homocysteine) were logarithmically (ln) transformed before analysis.

The prevalence of SWS was compared between participants with a history of a stroke and those without such a history after adjustment for age (40-49, 50-59, 60-69, 70-79, and ≥ 80 yrs), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, others), and by sex. After the persons who reported a history of stroke (n = 471) were excluded, multiple regression analysis was then performed to examine differences in cardiovascular risk profiles between those who had experienced only one (G2) or more SWS (G3) and those who had never experienced any SWS (G1). The analyses were adjusted for age, sex, and race/ethnicity. To adjust for multiple-group testing, a P of less than 0.017 was regarded as statistically significant considering type 1 error set at alpha = 0.05. Serum triglyceride, low-density lipoprotein (LDL) cholesterol, insulin, plasma glucose, LAP, and diagnosis of diabetes were available only for those who had fasted at least 8 hours before their laboratory examination in the morning. Therefore, distinct sample weights associated with the morning fasting sub-population were used for these variables.

The analysis was performed using SAS-callable SUDAAN 9.0 (Release 9.0.1, Research Triangle Institute, Research Triangle Park, North Carolina, 2007) to account for the complex sampling design.

RESULTS

An estimated 16.0% of US adults aged 40 years and over had experienced one SWS, and 11.0% had experienced more than one SWS. The prevalence of a history of stroke was 3.7% (95% CI: 3.2% to 4.2%). An estimated 10.5% (95% CI: 9.2% to 12.0%) of persons who had experienced SWS had a history of stroke, versus 1.0% (95% CI: 0.8% to 1.4%) of persons who had not experienced SWS. After excluding those with a history of stroke, an estimated 16% of US adults aged 40 or above had experienced one and 10% had experienced more than one SWS. After controlling for age and race/ethnicity, men with a history of stroke were not significantly more likely to have experienced SWS than were their female counterparts; however, men without a history of stroke were less likely to have experienced SWS than were women without this history (p = 0.0004) (Table **1**).

Among persons without a history of stroke, in a comparison with those who had never experienced SWS (G1), persons who had experienced one (G2) or more SWS (G3) manifested greater prevalence of cardiovascular diseases, higher levels of glycated hemoglobin, serum insulin, diastolic blood pressure, BMI, waist circumference, waist-to-hip ratio, serum triglycerides, LDL cholesterol, ratio of total to high-density lipoprotein (HDL) cholesterol, LAP, C-reactive protein, and fibrinogen and lower levels of HDL cholesterol (Table **2**). These persons were also more likely to be taking antihypertensive or cholesterol-lowering medications. There were no significant differences in systolic blood pressure, total blood cholesterol concentrations, serum uric acid, creatinine, or homocysteine concentrations between persons who had and had not experienced SWS. Compared with G2, the respondents in G3 manifested even greater prevalence of other cardiovascular diseases, higher levels of waist circumference, fasting serum insulin, percent glycated hemoglobin, and serum C-reactive

Table 1. Prevalence of Stroke Warning Symptoms Among Adults Aged 40 Years and Over with a History of Diagnosed Stroke and those without such a History (n = 9728) by Sex*

Symptom	History of Stroke					
	Yes			No		
	Men (n = 236)	Women (n = 230)	P for Difference	Men (n = 4422)	Women (n = 4840)	P for Difference
Weakness/paralysis of face, arm, leg for >5min, %	42.5 (4.8)	47.3 (4.5)	0.33	5.8 (0.5)	6.6 (0.5)	0.24
Numbness on one side of face/body for >5 min, %	51.9 (6.1)	52.8 (5.1)	0.82	9.7 (0.7)	11.5 (0.8)	0.15
Loss of vision in one/both eyes for >5 min, %	42.7 (5.9)	36.9 (4.1)	0.70	8.5 (0.6)	10.7 (0.8)	0.025
Severe dizziness for more than 5 minutes, %	27.3 (4.5)	34.5 (4.7)	0.23	8.9 (0.8)	14.3 (0.9)	0.0000
Problem with ability to speak/understand, %	41.9 (6.1)	35.4 (3.9)	0.37	2.7 (0.3)	3.7 (0.5)	0.08
Experience of one symptom, %	18.6 (4.6)	22.9 (5.4)	0.61	14.1 (1.0)	17.1 (0.9)	0.0004
Experience of two or more symptoms, %	64.5 (6.3)	55.8 (5.6)	0.61	7.5 (0.7)	11.0 (1.1)	0.0004
Mean number of symptoms	1.74 (0.12)	1.70 (0.13)	0.98	0.34 (0.02)	0.45 (0.02)	0.0001

* The parameters are expressed as adjusted estimates (standard error). All comparisons were controlled for age and race/ethnicity.

protein. In addition, The respondents in G3 were more likely to be taking hypertensive and cholesterol-lowering medication than those in G1 and G2. Nonetheless, respondents in G3 were younger (than those in G2), more likely to be women and non-whites.

DISCUSSION

The prevalence of individuals who have experienced one or more stroke warning symptoms in both the general and the stroke-free population aged 40 years and over was high (with estimates of 28% and 26%, respectively). Persons who experienced these symptoms manifested more adverse cardiovascular profiles than persons who had never experienced any such symptoms regardless of whether they had a history of diagnosed stroke. These findings potentially have important public health and clinical implications.

Some of the individuals who had experienced sudden SWS that lasted more than 5 minutes but never obtained a diagnosis of stroke may have had a transient ischemic attack (TIA). A TIA can be defined as "a brief episode of neurological dysfunction caused by a focal disturbance of brain or retinal ischemia, with clinical symptoms typically lasting less than 1 hour, and without evidence of infarction."[13] The incidence rates for TIA range from 68.2 to 83 per 100,000 in population studies [3]. After such an event, the 90-day risk of stroke is 3% to 17.3%, with up to a quarter of patients dead within a year [3]. In addition, those who suffer a TIA have a 10-year stroke risk of 18.8% and a combined 10-year risk for stroke, myocardial infarction (MI), or vascular death of 42.8% [3]. Most recently, a more inclusive term, "transient neurological attacks (TNAs)," has been proposed to define temporary (<24 hours) attack of neurological symptoms. These symptoms can be focal (i.e., TIA), non-focal, or a mixture of the two. In our study, the SWS included not only focal symptoms but also non-focal symptoms such as confusion, dizziness, and bilateral weakness. A large longitudinal study indicated that both focal and non-focal TNAs were associated with a higher risk of major vascular diseases, including stroke, ischemic heart disease, and vascular death [7]. These are coincident with our findings from NHANES that persons who experienced SWS indeed manifested more adverse cardiovascular profiles.

Approximately half of patients who experience a TIA fail to report it to their health care providers [14, 15], and it is thus very likely that some people who experience SWS in the presence of an actual TIA or stroke are never diagnosed with either of those disorders. In addition, almost half of stroke-related deaths occur before the patient reaches the hospital [16]. Many of these deaths and significant disability could be prevented if patients suffering SWS were aware they might be having a stroke and sought earlier treatment [3]. A Healthy People 2010 objective includes increasing public awareness of the warning signs of stroke [17]. Data from the Behavioral Risk Factor Surveillance System (BRFSS) indicated that public recognition of major SWS is low [18, 19]. Especially, persons at the highest risk of having a stroke — the elderly and those who have had a previous stroke — are less likely to know the warning signs of stroke [18]. Our analysis also indicated that the group (G3) of individuals who experienced more than two stroke warning symptoms may contain disproportionally more racial/ethnic minority women with a clustering of cardiovascular risk factors represented by central adiposity, dyslipidemia, hypertension, hyperinsulinemia and elevated inflammatory markers. These individuals may be at highest risk for stroke or other cardiovascular events in the future. Unfortunately, awareness and knowledge about stroke is suboptimal among American women, especially among racial/ethnic minorities [20]. Clearly, more efforts are needed to improve awareness among general public, those at high risk and among health care professionals. A high-intensity public education campaign can increase community awareness of the warning signs for stroke and the need to call 911 [21].

Although SWS does not necessarily lead to a stroke event immediately, persons who have experienced SWS are likely to have an adverse cardiovascular risk profile which confers an excess risk of stroke and other cardiovascular events in the long run. Therefore, they should seek further assessment of cardiovascular risk factors. The American Heart Association guidelines [22-25] have provided evidence-based

Table 2. Adjusted Prevalence or Mean (Standard Error) of Cardiovascular Risk Variables among Adults Aged 40 Years and Older without a History of Diagnosed Stroke by Lifetime Experience with Stroke Warning Symptoms

Cardiovascular Risk Variable	Sample Size †	G1: No Experience of the Symptoms (n = 6750)	G2: Lifetime Experience of One Symptom (n = 1482)	G3: Lifetime Experience of Two or More Symptoms (n = 1030)	P for Difference	
					G1 vs G2 & G3	G1 & G2 vs G3
Categorical Variables						
Women, %	9262	51.7 (0.8)	58.3 (1.9)	62.2 (2.8)	<0.0001	0.033
Whites, %	9262	80.8 (1.3)	83.1 (1.4)	74.4 (2.6)	0.19	0.0010
Prevalence of other cardiovascular disease, %	9262	12.0 (0.6)	20.9 (1.6)	38.2 (2.4)	<0.0001	<0.0001
Prevalence of diabetes, %	4083	17.7 (1.1)	20.4 (2.3)	24.2 (3.1)	0.023	0.08
Current smoker, %	9262	24.6 (1.0)	30.8 (2.0)	29.2 (1.9)	0.0039	0.54
Taking antihypertensive medication, %	9262	19.7 (0.7)	22.0 (1.4)	28.4 (1.8)	<0.0001	0.0007
Taking cholesterol-lowering medication, %	9262	4.3 (0.4)	5.7 (1.0)	9.6 (1.4)	0.0039	0.0014
Continuous Variables						
Age, yr	9262	56.7 (0.4)	59.3 (0.6)	57.6 (0.6)	0.0007	0.48
BMI, kg/m^2	9229	27.1 (0.1)	27.4 (0.3)	28.0 (0.3)	0.0092	0.029
Waist circumference, cm	8735	95.3 (0.3)	96.4 (0.7)	98.0 (0.7)	0.0002	0.01
Waist-hip ratio	8724	0.935 (0.002)	0.942 (0.003)	0.951 (0.003)	<0.0001	0.0006
Fasting serum insulin, ln uU/mL	3936	2.381 (0.017)	2.433 (0.031)	2.540 (0.049)	0.0005	0.0067
Fasting plasma glucose, ln mg/dL	4083	2.104 (0.031)	2.192 (0.083)	2.267 (0.100)	0.04	0.24
Percent glycated hemoglobin	8935	5.57 (0.03)	5.67 (0.04)	5.71 (0.05)	0.0002	0.068
Systolic blood pressure, mmHg	8873	127.1 (0.4)	126.1 (0.9)	126.3 (0.7)	0.31	0.91
Diastolic blood pressure, mmHg	9241	96.0 (3.0)	106.6 (5.3)	118.7 (9.4)	0.0027	0.046
Total serum cholesterol, mmol/L	8834	5.62 (0.02)	5.61 (0.05)	5.68 (0.05)	0.54	0.34
Serum HDL cholesterol, mmol/L	8763	1.33 (0.01)	1.30 (0.02)	1.27 (0.02)	0.014	0.064
Serum LDL cholesterol, mmol/L	3787	3.50 (0.03)	3.60 (0.05)	3.62 (0.07)	0.0078	0.27
Ratio of total serum cholesterol to HDL cholesterol	8760	4.64 (0.05)	4.74 (0.10)	4.81 (0.07)	0.028	0.16
Serum triglycerides, ln mmol/L	3909	0.926 (0.012)	0.958 (0.024)	0.975 (0.024)	0.038	0.26
Lipid accumulation product (LAP, ln)	3752	3.831 (0.028)	3.928 (0.049)	4.043 (0.052)	0.0008	0.012
Serum Uric acid, umol/L	8710	322.7 (1.6)	325.2 (4.1)	326.5 (5.0)	0.37	0.64
Serum creatinine, ln mg/dL	8709	0.734 (0.002)	0.737 (0.003)	0.741 (0.004)	0.10	0.19
Serum C-reactive protein, ln mg/dL	8768	0.316 (0.006)	0.337 (0.011)	0.382 (0.017)	0.0002	0.0036
Plasma fibrinogen, ln mg/dL	8619	3.023 (0.029)	3.057 (0.035)	3.128 (0.046)	0.030	0.061
Serum homocysteine, ln umol/L	3834	2.351 (0.014)	2.368 (0.022)	2.431 (0.040)	0.056	0.089

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
* The estimates were adjusted for sex, age, and race/ethnicity. † Sample size for each variable may not add up to total sample size because of missing values or because some variables were available only from the morning fasting sample.

recommendations for the control of risk factors (hypertension, diabetes, lipids, cigarette smoking, obesity, physical activity, etc.) and special approaches for implementation of the guidelines and their use in high-risk populations. Depending on clinical presentation, several tests may rule out conditions other than stroke or TIA that have symptoms similar to SWS, including hypoglycemia, complicated migraine [8], and Bell's palsy. Further, imaging techniques (carotid Doppler, carotid artery angiography, and computed tomography [CT] scans) and ECG may also help to identify underlying reasons for the symptoms and evaluate the subsequent risk of stroke [26].

The age-adjusted death rate for stroke has declined 70% since 1950. This decline is likely a result of better control of risk factors, improved access to early detection, and better treatment and care [2]. The impressive decline in the death rate notwithstanding, stroke remains the third-leading cause of death in the US and may be exacerbated by deleterious trends in obesity and diabetes. Being aware of stroke warning symptoms and seeking immediate medical attention thus become more imperative, as they give the best chance of a good outcome.

There are some limitations in this study. First, NHANES only capture stroke survivors so our study probably underestimates the significance of SWS. Second, The NHANES III questions we selected for our SWS group were among a larger group of questions regarding cardiovascular symptoms developed for the London School of Hygiene Cardiovascular Questionnaire [27]. Besides these symptoms, "sudden severe headache with no known cause" is also believed to be one of the common stroke warning symptoms

(see http://www.strokeassociation.org/). However, there was no "sudden severe headache" question included in the NHANES III questionnaire. Furthermore, the questions do not contain less common stroke warning symptoms.

The major strength of this study is the use of a large, population-based survey and its uniformly collected laboratory and examination data. The history of cardiovascular disease was well ascertained by a wide array of questions and ECG findings. A comprehensive set of cardiovascular risk markers were included for comparison purpose.

In conclusion, the warning symptoms of stroke may be a useful subjective screening tool to identify men and women who are vulnerable to stroke and other cardiovascular events. The data support the need for targeted educational programs to improve awareness of stroke risk and symptoms among general public. The individuals who have experienced the symptoms of stroke should be encouraged to see a physician to identify the underlying reasons for the symptoms and thus have a chance to be offered appropriate diagnosis and intervention.

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