Hypertensive Retinopathy and Risk of Cardiovascular Diseases in a National Cohort

Abstract

Background: Retinal vascular examination using direct ophthalmoscopy can be used to determine the extent of hypertensive vascular changes. We studied the association of these changes in a large national cohort.

Methods: First National Health and Nutrition Survey (NHANES I) was conducted from 1971 through 1975. A subgroup (n=5500) of participants aged 25 to 74 years received standardized ophthalmologic examination and hypertensive changes were documented. Participants of the study had follow-up interviews and examinations up to 1992. All health care facility records and death certificates were ascertained and reviewed. Participants who were admitted with or died of primary diagnosis of either ischemic stroke or coronary heart disease were identified. We used Cox proportional-hazards regression to study the association of hypertensive retinopathy with cardiovascular disease.

Results: After excluding patients with previous history of stroke or myocardial infarction and/or missing blood pressure information, 4753 participants were included in the analysis. Participants with hypertensive retinopathy were older (61 ± 11 vs 47 ± 15) and more likely to be men (54% vs 62%). After adjustment for age, sex, race/ethnicity, body-mass index, cigarette smoking, systolic blood pressure, cholesterol, and diabetes mellitus patients with hypertensive retinopathy had a relative risk (RR) of 1.2 (95% confidence interval [CI] 1.0 – 1.3) for any cardiovascular disease and RR of 1.2(95% CI 0.9-1.5) for ischemic stroke.

Conclusion: The presence of hypertensive retinal vascular changes is associated with increased risk of cardiovascular disease. Identification of such changes in the clinical setting can be used for stratification of high risk patients.

Keywords: Epidemiological survey; stroke; myocardial infarction; retinopathy; ophthalmological examination

Journal of Vascular and Interventional Neurology 2008; 1(3):75-78

M Fareed K Suri, MD
Adnan I Qureshi, MD

Address correspondence to:
M Fareed K Suri, MD, Zeenat Qureshi Stroke Research Center, Department of Neurology, University of Minnesota, 420 Delaware St SE, Minneapolis, MN 55455
fareedsuri@gmail.com

Retinal examination provides a readily available, noninvasive visualization of blood vessels. Retinal vessels have been suggested to mimic cerebral vasculature.[1, 2] Recently, association of retinal microvascular abnormalities with stroke has been noted in multiple studies[3-8] and the potential of their utilization in clinical and epidemiological setting is being realized.[9] However, further replication of these findings in other databases is needed.[9] We report the association of retinal vascular disease with incidence of cardiovascular diseases, ischemic stroke and myocardial infarction in a nationally representative cohort study.

Methods

We used data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS). NHANES I was conducted by the National Center for Health Statistics from 1971 through 1975 to collect health-related information on a nationally representative probability sample of the US civilian non-institutionalized population. To increase the sample size in select subgroups, the survey over-sampled the elderly, persons living in poverty areas, and women of childbearing age. The NHANES I Epidemiologic Follow-up Study (NHEFS) was jointly initiated by the National Center for Health Statistics and the National Institutes of Health. The objective of the NHEFS was to follow up the 14,407 participants in the NHANES I who were between the ages of 25 and 74 years at the time of that survey and completed a baseline medical examination. Data collection for this analysis included tracing all NHANES I participants for morbidity and mortality through 1992 using health care facility (hospital or nursing home) records or death certificates. The NHEFS included four followup waves, 1982-1984, 1986, 1987, and 1992.
We used 20-year follow-up data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS) to determine the risk of stroke and myocardial infarction in middle aged and elderly persons.

Definition of incident cardiovascular events.

From the Zeenat Qureshi Stroke Research Center, University of Minnesota, Minneapolis, MN

Dr. Suri and Dr. Qureshi, both JVIN contributing editors, were not involved in the editorial evaluation or decision to publish this article.

We defined incident ischemic stroke (n=309) cases as study participants who were hospitalized or died during the 20-year follow-up period with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 433-434.9 or 436-437.1. Individuals with ICD-9-CM code 435 (transient ischemic attack, TIA) were not included as incident stroke cases. Persons with ICD-9-CM codes 410-414 were defined as having coronary artery disease (CAD) (n=798). ICD-9-CM codes for deaths were based on the underlying cause of death listed on the participant's death certificate.

Definition of hypertensive retinopathy.

A subgroup (n=5500) of participants aged 25-74 years, received a standardized ophthalmologic examination at baseline. Retinoscopy was done for examinees with visual acuity less than 20/40. Up to 10 diagnoses using Centers for Disease Control and Prevention (CDC) Ophthalmologic Disease Code (ODC), were listed for each examinee. Hypertensive arteriolar sclerosis, macular involvement, arteriovenous nicking, or any arteriosclerosis was classified as hypertensive retinopathy (ODC codes 76-35-64, and 76-00-00).

Study variables.

Potential confounders in the association between hypertensive retinopathy and cardiovascular disease were age, sex, ethnicity (black, white, other), serum cholesterol level, body mass index (weight [kg]/height [m2]) (>30.0), diabetes mellitus, cigarette smoking (never, former, current), and systolic blood pressure. All measures were obtained prospectively during the NHANES I baseline interview. Smoking status was self-reported.

Diabetes mellitus was determined by patient selfreport or by

Table 1. Baseline demographic and clinical characteristics of participants in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS). (1971-1975)

		No hypertensive retinopathy (n=3818)	Hypertensive retinopathy (n=935)
Age (mean ± SD) in years		47 ± 15	61 ± 11*
Gender			
	Men	1442 (38%)	428 (46%)
	Women	2376 (62%)	507 (54%)*
Race/Ethnicity			
	Caucasian	3032 (79%)	618 (66%)
	African-American	746 (20%)	306 (33%)*
	Others	40 (1%)	11 (1%)
Diabetes Mellitus			
	Diabetic	125 (3%)	65 (7%)
	Non-diabetic	3693 (97%)	870 (93%)*
Cigarette smoking			
	Current	955 (25%)	114 (12%)
	Past	785 (21%)	203 (22%)*
	Unknown	599 (16%)	181 (19%)*
	Never	1479 (39%)	437 (47%)*
Systolic blood pressure (mean ± SD) in mmHg		132 ± 23	150 ± 26*
Body mass index (mean ± SD) in units		25.5 ± 5	26.6 ± 5.6*
Serum cholesterol (mean ± SD) in mg/dl		217 ± 47	232 ± 51*

*p<0.05 (t-test or Chi-square test); Abbreviations used: SD, standard deviation

physician coding. Measurements of height and weight were taken by trained examiners during the NHANES I physical examination.

Statistical analysis.

Because the interval of follow-up varied among study participants, Cox proportional hazards analysis was used to estimate the relative risk for stroke and coronary heart disease. The Cox proportional hazards assumptions for each explanatory variable were assessed with the SPSS. The multivariate adjusted Cox proportional hazards model adjusted for differences in age, sex, ethnicity, cigarette smoking, systolic blood pressure, serum cholesterol level, diabetes mellitus, and body mass index.

Results

A total of 5500 persons aged 25-74 years underwent a detailed interview and ophthalmologic examination in the NHANES I baseline survey. Follow-up was available for 5155 persons. A total of 402 persons were excluded because of a previous history of stroke or myocardial infarction (n=376), and/or missing blood pressure information (n=26). During the follow-up period, the rate of CAD and ischemic stroke was 798 (17%) and 309 (7%), respectively. The baseline characteristics of the participants according to retinal changes are provided in Table 1. The participants with hypertensive retinopathy were older and had higher systolic blood pressure, body mass index, and serum cholesterol. The proportion of women, African-Americans, non-diabetics, past or non-smokers was higher in the participants with hypertensive retinopathy.

Table 2 provides the event rate, age- and multivariate adjusted relative risk of cardiovascular diseases, CAD, and ischemic stroke according to the retinal changes of the patients. The risk of all cardiovascular diseases was increased in persons with hypertensive retinopathy (relative risk [RR], 1.2; 95% confidence interval [CI], 1.0 – 1.3). The age- adjusted risks of both ischemic heart disease (RR 1.2, 95% CI 1.0-1.4) and ischemic stroke (RR 1.3, 95% CI 1.0 -1.6) were higher among persons with hypertensive retinopathy. A trend towards higher risk was observed for both CAD and stroke with retinal vascular disease after adjusting for other confounding factors.

Discussion

In this study, we noted that hypertensive retinal changes were associated with an increased risk of cardiovascular diseases independent of other cardiovascular risk factors. When analyzed separately, there was a trend towards increased risk of both stroke and CAD associated with hypertensive retinopathy. Retinal vascular changes in patients with elevated blood pressure have long been recognized and their detection is recommended in clinical practice.[10] Although the similarities between retinal and cerebral circulation have been known[1, 2], there was little information on the prognostic implications of these findings. Recently, data from cohort studies have identified independent association of these findings with cardiovascular disease. The Atherosclerosis Risk in Communities (ARIC) study demonstrated that the presence of any retinopathy increases the risk of stroke by 2.6 times over an aver age followup of 3.5 years.[3] This risk was independent of age, sex, ethnicity, mean arterial pressure, use of antihypertensive medication, diabetic status, and cholesterol level. Duncan et al[11] studied 560 hypertensive middle aged men for a median follow-up of 7.8 years. Presence of hypertensive retinopathy doubled the risk of definite coronary heart disease events independent of other cardiovascular risk factors. Wong et al[4] studied the 10 year risk of cardiovascular mortality in a population-based study with nested case-control design and noted that, independent of other cardiovascular risk factors,

Table 2. The 20-year risk of cardiovascular disease according to retinal vascular changes among participants in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS). Multivariate analysis adjusted for age, sex, race/ethnicity, body-mass index, cigarette smoking, systolic blood pressure, serum cholesterol, and diabetes mellitus.

Participants	Sample size	No of events	Event rate per 100	Age-adjusted relative risk (95% CI)	Multivariate-adjusted relative risk (95% CI)
Cardiovascular diseases					
No vascular retinal changes	3818	682	17.9	Reference	Reference
Hypertensive retinopathy	935	331	35.4	1.2 (1.0 – 1.4)	1.2 (1.0 – 1.3)
Ischemic heart disease					
No vascular retinal changes	3818	545	14.3	Reference	Reference
Hypertensive retinopathy	935	253	27.1	1.2 (1.0 – 1.4)	1.1 (0.97 – 1.3)
Ischemic stroke					
No vascular retinal changes	3818	193	5.1	Reference	Reference
Hypertensive retinopathy	935	116	12.4	1.3 (1.0 – 1.6)	1.2 (0.9 – 1.5)

Abbreviations used: CI, confidence interval

retinopathy was associated with an increased risk of cardiovascular mortality(odds ratio 1.8).

Mitchell et al studied association of retinopathy in 859 subjects without diabetes mellitus who were followed for 7 years.[12] After controlling for cardiovascular risk factors, retinopathy was significantly associated with risk of incident stroke/TIA/cerebrovascular death (Relative risk 1.7). Our study supports the findings of these studies and with larger sample size and longer follow-up duration.

The association between retinopathy and magnetic resonance imaging (MRI) findings in the brain has been previously noted. The incidence of white matter lesions in persons with retinopathy was 22.9% compared with 9.9% in persons without retinopathy in ARIC study.[13] Cooper et al[6] in a cross-sectional study noted that persons with retinal microvascular abnormalities, independent of other risk factors, have odds of 1.9 for having cerebral infarcts on MRI compared to those without these changes.

Recently, an analysis from Cardiovascular Health Study (CHS) noted association between MRI findings and smaller retinal arteriovenous ratio independent of age, gender, hypertension and diabetes mellitus.[7]

The association between retinal vascular changes and cardiovascular disease is based on the hypothesis that retinal vasculature provides direct visual assessment of the hypertensive or other pathological changes affecting the vasculature. Some pathophysiological studies have supported this hypothesis. Thickening of retinal artery has been noted to be associated with fibrinoid degeneration, fibrous nodules, and splitting of cerebral vessels.[2] Lower arteriolar-to-venular ratio in retina has also noted to be related to increased carotid intima-media thickness[14].

Retinal vascular examination as a predictor of cardiovascular events has important implications. The abnormalities can be used to help identify patients at higher risk of cardiovascular disease, both in clinical and epidemiological settings. There is some evidence to suggest that these changes can even be reversed.[15] If this reversal accompanies reduction of cardiovascular risk, then this can serve as a surrogate marker for treatment efficacy. Retinal photography has improved the inter-rater reliability and is now becoming a standard tool for retinal vascular epidemiological studies. Our study was limited because of lack of more advanced methodologies for detecting retinal vascular changes. The number of patients with untreated or uncontrolled hypertension among general population is lower now compared to the study period.[16]

Hypertensive retinopathy definition, in comparison to direct ophthalmoscopic findings used in our study, is based on retinal photography in recent studies. This allows more accurate measurement of blood vessel diameters.[9] A large sample size, a nationally representative population, and long follow-up duration are the strengths of our study.

In conclusion, this study confirms the association between hypertensive retinopathy and cardiovascular disease and supports the idea of routine inclusion of these findings in cardiovascular-risk stratification.

Acknowledgements

Dr. Suri is supported by National Institute's of Health (NIH) grant 5K12-RR023247-03. Dr. Qureshi is supported in part by NIH's grant RO-1-NS44976-01A2 and the American Heart association's Established Investigators Award 0840053N.

References

1. Hickam JB, Schieve JF, Wilson WP. The Relation between Retinal and Cerebral Vascular Reactivity in Normal and Arteriosclerotic Subjects. Circulation 1953;7:84-87.
2. Goto I. Pathological Studies on the Intracerebral and Retinal Arteries in Cerebrovascular and Noncerebrovascular Diseases.Stroke 1975;6:263-269.
3. Wong T, Klein R, Couper D, Cooper L, Shahar E, Hubbard L, Wofford M, Sharrett A. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. The Lancet. 2001;358:1134-1140.
4. Wong T, Klein R, Nieto F, Klein B, Sharrett A, Meuer S, Hubbard L, Tielsch J. Retinal microvascular abnormalities and 10-year cardiovascular mortality A population-based case-control study. Ophthalmology 2003; 110:933-940.
5. Klein B, Klein R, McBride P, Cruickshanks K, Palta M, Knudtson M, Moss S, Reinke J. Cardiovascular Disease, Mortality, and Retinal Microvascular Characteristics in Type 1 Diabetes Wisconsin Epidemiologic Study of Diabetic Retinopathy. Am Med Assoc 2004;164:1917-1924.
6. Cooper LS, Wong TY, Klein R, Sharrett AR, Bryan RN, Hubbard LD, Couper DJ, Heiss G, Sorlie PD. Retinal Microvascular Abnormalities and MRI-Defined Subclinical Cerebral Infarction: The Atherosclerosis Risk in Communities Study. Stroke 2006;37:82-86.
7. Longstreth Jr W, Larsen E, Klein R, Wong T, Sharrett A, Lefkowitz D, Manolio T. Associations between Findings on Cranial Magnetic Resonance Imaging and Retinal Photography in the Elderly: The Cardiovascular Health Study. American Journal of Epidemiology 2007; 165:78.
8. Kobayashi S, Okada K, Koide H, Bokura H, Yamaguchi S. Subcortical Silent Brain Infarction as a Risk Factor for Clinical Stroke. Stroke 1997; 28:1932.
9. Yin Wong T. Is retinal photography useful in the measurement of stroke risk? Lancet Neurology 2004; 3:179-183.
10. Chobanian A, Bakris G, Black H, Cushman W, Green L, Izzo J, Jones D, Materson B, Oparil S, Wright J. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure The JNC 7 Report. Am Med Assoc 2003;289:2560-2571.
11. Duncan B, Wong T, Tyroler H, Davis C, Fuchs F. Hypertensive retinopathy and incident coronary heart disease in high risk men. BMJ; 2002;86:1002-1006.
12. Mitchell P, Wang J, Wong T, Smith W, Klein R, Leeder S. Retinal microvascular signs and risk of stroke and stroke mortality. Neurology 2005; 65:1005-1009.
13. Wong T, Klein R, Sharrett A, Couper D, Klein B, Liao D, Hubbard L, Mosley T. Cerebral White Matter Lesions, Retinopathy, and Incident Clinical Stroke. Am Med Assoc 2002;288:67-74.
14. Ikram M, de Jong F, Vingerling J, Witteman J, Hofman A, Breteler M, de Jong P. Are Retinal Arteriolar or Venular Diameters Associated with Markers for Cardiovascular Disorders? The Rotterdam Study. Investigative Ophthalmology & Visual Science 2004;45:2129-2134.
15. Bock K. Regression of retinal vascular changes by antihypertensive therapy. Hypertension. 1984; 6:62
16. Qureshi A, Suri M, Kirmani J, Divani A. Prevalence and trends of prehypertension and hypertension in United States: National Health and Nutrition Examination Surveys 1976 to 2000. Medical Science Monitor(online) 2005; 11.Available at www.medscimonit.com.