Incidental Asymptomatic Intracerebral Hemorrhages and Risk of Subsequent Cardiovascular Events and Cognitive Decline in Elderly Persons

Adnan I. Qureshi, MD, Morad Chughtai, MD, Ahmed A. Malik, MD, Cara Bezzina, MD, and M. Fareed K. Suri, MD

Background: The long-term prognostic significance of incidental asymptomatic intracerebral hemorrhages (aICHs) detected on brain magnetic resonance imaging (MRI) is unknown. *Methods:* We analyzed clinical and baseline MRI data from the cohort of 5888 study participants aged 65 years and older recruited in the Cardiovascular Health Study from 4 US communities. We identified participants who had aICHs on MRI and selected 3 age- and gender-matched controls without aICHs. We compared the rates of cardiovascular events using logistic regression analysis including incident myocardial infarction, stroke, and death between those with and without aICHs. *Results:* A total of 23 participants had aICHs classified as acute (n = 3), subacute (n = 4), and chronic (n = 16). During 14 years of follow-up, the risk of incident stroke (relative risk [RR], .6; 95% confidence interval [CI], .2-2.0), myocardial infarction (RR, .3; 95% CI, .06-1.4), and death (RR, .6; 95% CI, .2-1.7) was not different between participants with aICHs compared with controls (n = 69). There was no difference between the 2 groups with regard to time to ischemic stroke or time to death by Kaplan–Meier analysis. *Conclusions:* The risks of stroke, myocardial infarction, and death were similar between persons with aICHs detected on MRI compared with age- and gender-matched controls. **Key Words:** Intracerebral hemorrhage—asymptomatic—cardiovascular events—epidemiologic study—stroke.

Incidental (asymptomatic) cerebral hemorrhages have been identified in healthy elderly persons and patients with ischemic stroke, intracerebral hemorrhage, and cerebral amyloid angiopathy.[1] The prevalence of asymptomatic intracerebral hemorrhages (aICHs) varied from 3.1% in Japanese adults (average age, 53 years),[2] 4.5% in the Framingham Study (average age, 64.4 years),[3] 6.4% in the Austrian Stroke Prevention Study (average age, 60 years),[4] 11.1% in the Reykjavik Study (mean age, 76 years),[5] and 15% in the Rotterdam Scan Study (mean age, 60.3 years).[6] The prevalence of aICHs increased with age, from 6.5% in persons aged 45-50 years to 35.7% in participants aged 80 years or older in the Rotterdam Scan Study.[6] The prevalence of aICHs is expected to increase because of the increase in population aged 80 years or older.[7] There is a paucity of data regarding the prognostic significance of such asymptomatic findings on magnetic resonance imaging (MRI)[1] unlike in patients with ischemic stroke or intracerebral hemorrhage.[8,9] aICHs detected in patients presenting with acute ischemic stroke or transient ischemic attack were associated with a 3-fold higher risk of subsequent disabling or fatal stroke within 18 months compared with patients without an aICH.[8] Higher numbers of aICHs at baseline predict an increased risk for subsequent

From the Zeenat Qureshi Stroke Institute, St. Cloud, Minnesota.
Received October 4, 2014; revision received December 10, 2014; accepted January 12, 2015.
Address correspondence to Adnan I. Qureshi, MD, Department of Cerebrovascular Diseases and Interventional Neurology, CentraCare Health System, 1406 6th Ave N, St Cloud, MN 56303. E-mail: qureshai@gmail.com.
1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.01.020

cognitive impairment, loss of independence, or death in patients with intracerebral hemorrhage.[9] We performed this study to determine the risk of cardiovascular events in elderly persons with aICHs on MRI using a case–control design.

Materials and Methods

We analyzed data from the cohort of 5888 study participants aged 65 years and older recruited in the Cardiovascular Health Study (CHS) from 4 US communities: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania.[10] Medicare eligibility lists from these 4 US communities were used to obtain a representative sample of 5201 community-dwelling elderly, who answered standardized questionnaires and underwent an extensive clinical examination at baseline.[11]

For each cardiovascular condition, self-reports were confirmed by components of the baseline examination or, if necessary, by a validation protocol that included either the review of medical records or surveys of treating physicians. The Modified Mini-Mental State Examination (MMSE) was also performed.[12] These tests were repeated annually during the CHS follow-up. CHS participants were invited to undergo magnetic resonance studies using a predefined standard protocol as described previously.[13] The MRI examinations included spin-density and T2-and T1-weighted spin-echo images with 5-mm thickness and zero gap and oriented parallel to the anterior–posterior commissure line. Images were read centrally by designated neuroradiologists.[14] The volume of aICH was measured using the ABC/2 method as previously described.[15] At the time of the MRI examination, a short history and neurologic examination were done by trained technicians who assessed gait, balance, visual fields, and strength in upper extremities. A summary of the neurologic examination findings was made by summing the number of abnormalities on both sides, which were then categorized as follows: no abnormalities; 1 or 2 abnormalities; 3 or 4 abnormalities; and 5 or 6 abnormalities (the maximum observed).[14]

Potential incident events, hospitalized and outpatient and all deaths, were investigated in detail based on initial identification through International Classification of Diseases (ICD-9) diagnostic codes or mention of an end point on the hospital face sheet, discharge summary, or outpatient procedure report.[11] Events were ascertained either through clinic visits or surveillance calls, when participants are asked to provide information on all hospitalizations and outpatient end point diagnoses since the last CHS contact. Secondary sources of events include identification of unreported earlier hospitalizations or outpatient end point diagnoses during review of medical records for a reported event and through the use of Medicare hospitalization data. Stroke during the study was ascertained by questions at the annual visit, interim telephone contacts, and review of hospitalizations. When notification of a possible stroke was received, medical and interview information was obtained and the occurrence of a stroke was determined by the Cerebrovascular Disease Adjudication Committee.[16] Strokes detected and confirmed after entry were referred to as "clinically recognized stroke" because adjudication protocols required supporting evidence of stroke such as signs, symptoms, or abnormalities on imaging. The 3 cardiac end points (myocardial infarction, angina, and congestive heart failure) were adjudicated by the cardiac subcommittee.[11] MMSE was repeated annually during the CHS follow-up.

Statistical Analyses

We used a case–control design; for each person with aICHs detected at baseline MRI, 3 age- and gender-matched controls were selected. Matching was done on the basis of age at screening, date of enrollment, gender, race/ethnicity (white, African American, Hispanic, and other), and absence of aICHs on MRI at baseline. The final sample size included 23 matched pairs. Baseline characteristics were summarized for cases and controls using mean and standard deviation (SD) values for normally distributed continuous variables and frequencies and percentages for categorical variables. Cumulative incidence of stroke or cardiac end points was calculated according to the Kaplan–Meier method, and incidence curves were compared with the log-rank test. A separate analysis of stroke and cardiac end points was performed. Incidence of cognitive decline (5-point or greater decline in scores over up to 3 years)[12] was also estimated in participants who had 2 cognitive tests performed.

Results

A total of 23 participants had aICHs classified as acute (n = 3), subacute (n = 4), and chronic (n = 16). The mean age ± SD was 75.2 ± 6.8 years and 16 were women. The location of aICHs was as follows: 12 on the left side and 11 on the right side. There were 6 lobar, 6 subcortical, 4 pons/midbrain, 4 cerebellar, and 3 basal ganglionic aICHs. The mean anterior–posterior dimension was 0.7 cm with a range of .2 cm-1.7 cm. The mean right-to-left dimension was 0.6 cm with a range of 0.3 cm-2.0 cm. The mean aICH volume was 0.3 cm^3 with a range of .1 cm^3-2.9 cm^3.

There were no differences in the proportion of participants with chronic hypertension (65.2% versus 71.0%) and previous stroke (8.7% versus 7.2%) between those with (n = 23) and without aICHs (n = 69). The initial systolic blood pressure (mean ± SD) was not significantly higher among participants with aICHs compared with those with no ICH (142.8 ± 22.6 versus 146.0 ± 17.4, $P = .5$). There were no differences in the proportion of