Hemostatic Markers and Long-Term Risk of Intracerebral Hemorrhage in Postmenopausal Women

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Background: Known risk factors for intracerebral hemorrhage (ICH) include age, hypertension, smoking, alcohol intake, and anticoagulant use. Some previous reports have indicated that hemostatic factors measured many years before the onset of ICH might predict the later occurrence of ICH. The objective of this analysis was to test whether selected hemostatic factors measured years before the onset of ICH could identify patients at higher risk for future ICH. *Methods:* We performed a nested case–control study within the Women's Health Initiative (WHI) cohort. Postmenopausal women aged 50-79 years (mean 68) at baseline (1993-1998) were enrolled at 40 Clinical Centers in the United States and followed for adjudicated ICH for a mean of 11.4 years. ICH cases (N = 75) and controls (N = 75) were matched on age, ethnicity, blood pressure, anticoagulant use, and treated hypertension. Stored blood samples from the baseline WHI examination were tested for von Willebrand factor (vWF), a disintegrin-like and metalloprotease domain with thrombospondin type-1 motif, number 13 (ADAMTS13), tissue plasminogen activator (t-PA), and urokinase plasminogen activator (u-PA). Platelet count, white blood cell count, and hemoglobin concentration were also measured. *Results:* Mean baseline levels of vWF (1.03 and .95 U/mL), ADAMTS13 (1.0 and 1.1 μg/mL), vWF : ADAMTS13 ratio (.99 and .92), t-PA (14.75 and 14.80 IU/mL), and u-PA (.09 and .10 IU/mL) were not significantly different by case–control status. Significant differences were also not identified for platelet count, hemoglobin, white blood count, or reported alcohol use. *Conclusion:* None of the 4 baseline hemostatic factors nor the platelet count was predictive of future ICH risk in this long-term study of older postmenopausal women. **Key Words:** Cerebral hemorrhage—von Willebrand factor—ADAMTS13—plasminogen activators.

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Introduction

Intracerebral hemorrhage (ICH) is a common and frequently devastating disorder that accounts for up to 20% of all strokes.[1,2] In contrast to ischemic stroke that is often preceded by transient ischemic attack, ICH typically has no identifiable premonitory symptoms. Notably, mortality and morbidity of ICH are high (up to 50% at 30 days). Therefore, efforts to identify high-risk individuals could be especially important and useful in developing early preventive approaches.[1-3] In this regard, previous studies have identified older age, higher alcohol intake, hypertension, male sex, current smoking, and diabetes as risk factors[4] for the development of ICH. Lower blood cholesterol and lower triglycerides have also been reported in association with higher risk of primary ICH.[5]

Several prior studies have suggested that hemostatic factors might also be related to subsequent occurrence of ICH. Consistent associations have been reported between ICH and use of anticoagulant agents.[3] Both warfarin[1,2,5] and aspirin[1,2,6] have been associated with an increased risk of ICH. Patients with inherited or acquired bleeding disorders also have a higher risk of ICH compared to those without bleeding disorders.[3,7-11] In long-term cohort studies, von Willebrand factor (vWF) has been examined in 2 studies, but results were inconsistent.[10,12] In 1 study, vWF was associated with higher risk of ICH,[10] but in the second study, higher levels of vWF were significantly associated with lower ICH risk.[12] A disintegrin-like and metalloprotease domain with thrombospondin type-1 motif, number 13 (ADAMTS13) cleaves vWF high–molecular-weight multimers, and has been implicated in bleeding associated with the acquired von Willebrand syndrome.[13] Either increases in ADAMTS13 or a decrease in the ratio of vWF to ADAMTS13 could predispose to hemorrhage. The administration of tissue plasminogen activator (t-PA) or urokinase plasminogen activator (u-PA) for the treatment of acute pulmonary embolism is associated with an increased risk for intracranial hemorrhage,[14] and higher levels of u-PA promote bleeding in patients with the Quebec platelet disorder.[15] Based on these previous studies, we hypothesized that higher levels of one or more of these hemostatic factors present years before an event might be predictive of subsequent ICH on long-term follow-up.

Materials and Methods

Study Population

The Women's Health Initiative (WHI) observational study was designed to investigate strategies for the prevention of common diseases among postmenopausal women, including cancers, cardiovascular diseases, and osteoporotic fractures.[6] Detailed methods for the WHI study have been reported.[6] Postmenopausal women aged 50-79 years at baseline (1994-1998) were enrolled at 40 Clinical Centers in the United States.[16] Overall 93,676 women participated in the observational study and were followed up for a mean of 16 years. For this analysis, the average follow-up time was 11.4 years (range: 4 months-18 years). The participants provided written informed consent.[6] The study was approved by the institutional review boards of the participating clinical centers: the WHI Coordinating Center at the Fred Hutchinson Cancer Research Center and the National Institutes of Health.[16]

Design

Overall, the present study was a nested case–control study utilizing WHI baseline data, detailed event follow-up, and stored baseline blood specimens. Repeat blood sampling during follow-up was not available.

Cases of ICH (N = 75) and controls without ICH (N = 75) were matched by the WHI Coordinating Center on baseline factors for age (within 2 years), ethnicity (black/white), systolic BP (within 10 mmHg), diastolic BP (within 10 mmHg), aspirin use (≥80 mg/day for 30 days as positive, yes/no), anticoagulant use (yes/no), or miscellaneous hematological drug use (antihemophilic products, platelet aggregation inhibitors, plasma expanders, plasma proteins, protamine, thrombolytic enzymes; yes/no), treated hypertension (yes/no), randomization clinic, blood draw dates (within 180 days), and follow-up time (control was required to have at least as much follow-up time as its matched case).

The exclusion criteria included patients who (1) were not white or African American; (2) had a history of cardiovascular disease (myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, stroke); (3) had missing baseline variables or event follow-up data; (4) had inadequate stored baseline citrated plasma; and (5) had stroke (controls).

All cases of intracerebral hemorrhagic stroke, defined in WHI as a stroke classified as "intraparenchymal hemorrhage" based on central adjudication after local event adjudication, were eligible for selection.[17] Matched controls were eligible among those who did not have an ICH. Per WHI protocol,[17] stroke was defined as (1) a rapid onset of persistent neurological deficit attributable to obstruction or rupture of the vascular system; (2) a deficit not known to be secondary to brain trauma, tumor, infection, or other cause; and (3) a deficit lasting for more than 24 hours, unless death supervenes or there is a demonstrable lesion compatible with acute stroke on computed tomography or magnetic resonance imaging scan. Stroke was further classified into 5 categories: (1) subarachnoid hemorrhage not resulting from a procedure, (2) ICH not resulting from a procedure, (3) other or unspecified intracranial hemorrhage not resulting from a procedure, (4) occlusion of the cerebral or precerebral arteries with infarction not resulting from a procedure, and (5) central nervous system complications during or resulting from