Von Willebrand Factor Drives the Association Between Elevated Factor VIII and Poor Outcomes in Patients With Ischemic Stroke

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Background and Purpose—Despite clear roles of factor VIII (FVIII) and von Willebrand factor (vWF) in thrombosis, few studies have examined the relationship of these factors with acute ischemic stroke (AIS). We sought to determine whether concurrent elevation in FVIII and vWF was associated with adverse events and outcomes.

Methods—From our prospective stroke registry, patients consecutively admitted with AIS between July 2008 and October 2013 were included if both FVIII and vWF were measured during admission. The primary outcome was the modified Rankin Scale score on discharge.

Results—Among 1453 cases in our stroke registry, 148 patients with AIS met inclusion criteria; 62 patients (41.9%) had FVIII−/vWF−, 16 patients (10.8%) had FVIII+/vWF−, and 51 patients (34.5%) had FVIII+/vWF+. In the fully adjusted model, patients with FVIII+/vWF+ had increased odds of inpatient complications (odds ratio, 8.6; 95% confidence interval, 1.58–46.85; \( P=0.013 \)) and neuroworsening (odds ratio, 3.2; 95% confidence interval, 1.18–8.73; \( P=0.022 \)) than patients with FVIII−/vWF−. Adjusted for age, baseline stroke severity, and glucose, patients with FVIII+/vWF+ had increased odds of poor functional outcome (modified Rankin Scale>2; odds ratio, 2.87; 95% confidence interval, 1.16–7.06; \( P=0.021 \)) than patients with FVIII−/vWF−.

Conclusions—Concurrent FVIII/vWF elevation predicts higher odds of inpatient complications, neuroworsening, and worse functional outcomes for patients with AIS compared with patients with normal levels. Our findings suggest that FVIII and vWF levels may serve as clinically useful stroke biomarkers by providing risk profiles for patients with AIS.

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Key Words: blood coagulation factors • factor VIII • stroke • thrombosis • von Willebrand factor

Factor VIII (FVIII), a protein heavily involved in clot formation, is biochemically stabilized in plasma by von Willebrand Factor (vWF). The FVIII–vWF complex supports FVIII binding and cleavage with other components of the coagulation cascade and mediates platelet attachment to damaged subendothelium.\(^1\) A relationship between levels of FVIII and vWF has been demonstrated.\(^2\)^\(^3\) Several studies support the association between elevation in either FVIII or vWF and increased risk of venous thrombosis and recurrent thromboembolic events.\(^4\)^\(^5\) Elevated FVIII is a risk factor for acute ischemic stroke (AIS) and coronary artery disease.\(^6\)^\(^9\) However, no evidence exists for the combined effect of FVIII and vWF in the context of AIS. In this study, we sought to determine differences in stroke severity, in-hospital complications, and outcomes between patients with normal serum values of FVIII and vWF and those with singular elevation in FVIII or combined elevation in both FVIII and vWF. In addition, we explored the relationship of singular elevation in vWF with these variables.

Methods

Patients who presented to our stroke center with AIS between July 2008 and October 2013 were identified consecutively from our prospective registry. Patients <18 years or who did not have FVIII and vWF levels obtained during admission were excluded.

Laboratory tests for hypercoagulability were ordered at the discretion of the treating physician, typically when no obvious cause of stroke was identified. The laboratory reference range for both FVIII and vWF is 50% to 150%. We defined elevated levels at the 200% threshold based on our previous research.\(^4\)

Patients were divided into 4 groups: both FVIII and vWF within normal range (FVIII−/vWF−); FVIII within normal range, but elevated vWF (FVIII+/vWF+); elevated FVIII, but normal vWF (FVIII+/vWF−); and elevation of both FVIII and vWF (FVIII+/vWF+).
Appropriate statistical tests and multivariate logistic regression analyses were conducted, including adjustment for age, National Institute of Health Stroke Scale (NIHSS), glucose level on admission, and administration of intravenous tissue-type plasminogen activator. Our institutional review board approved this study.

### Results

#### Patient Demographics and Baseline Characteristics

Among 1453 AIS cases, 148 patients met criteria; 62 patients (41.9%) had FVIII−/vWF−, 19 patients (12.8%) had FVIII−/vWF−.

| Table 1. Demographic and Baseline Characteristics of Patients According to Factor VIII and vWF Levels |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Normal Factor VIII | Normal Factor VIII | Elevated Factor VIII (>200%) | Elevated Factor VIII (>200%) |
| Normal vWF | n=62 (41.9%) | n=19 (12.8%) | n=16 (10.8%) | n=51 (34.5%) |
| Demographic info | | | | PValue |
| Age, median (range) | 53 (26–83) | 54 (19–85) | 56 (23–77) | 54 (22–78) | 0.317 |
| Black, n (%) | 43 (69.4) | 15 (79.0) | 10 (62.5) | 41 (80.4) | 0.520 |
| Female, n (%) | 23 (37.1) | 9 (47.4) | 9 (56.3) | 32 (62.8) | 0.052 |
| History of hypertension, n (%) | | | | |
| Prior h/o stroke | 20.0 (32.3) | 8.0 (42.1) | 10.0 (62.5) | 17.0 (34.0) | 0.143 |
| Hyperlipidemia | 10.0 (16.1) | 10.0 (52.6)* | 8.0 (50.0)* | 12.0 (24.0) | 0.002 |
| History of DM | 12.0 (19.4) | 9.0 (47.4)* | 7.0 (46.7)* | 24.0 (49.0)* | 0.005 |
| History of hypertension | 41.0 (66.1) | 17.0 (89.5) | 12.0 (75.0) | 37.0 (74.0) | 0.247 |

Admission information/visit history (baseline values)

| Normal Factor VIII | Normal Factor VIII | Elevated Factor VIII (>200%) | Elevated Factor VIII (>200%) |
| Laboratory values (only significant values reported) | | | PValue |
| CRP value, median (range) | 0.40 (0.03–2.20) | 2.3 (0.3–8.8) | 4.7 (1.0–11.1)* | 2.3 (0.3–12.1)* | 0.010 |
| ESR rate, median (range) | 10 (0–106) | 13 (2–56) | 18 (6–151) | 28 (2–139) | 0.009 |

#### Table 2. Laboratory/Outcome Characteristics of Patients by Factor VIII and vWF Levels

| Normal Factor VIII | Normal Factor VIII | Elevated Factor VIII (>200%) | Elevated Factor VIII (>200%) |
| Laboratory values (only significant values reported) | | | PValue |
| CRP indicates C-reactive protein; d/c, discharge; ESR, erythrocyte sedimentation rate; FVIII, factor VIII; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; and vWF, von Willebrand factor. |

*P<0.05 compared with FVIII−/vWF−.
vWF+, 16 patients (10.8%) had FVIII+/vWF−, and 51 patients (34.5%) had FVIII+/vWF+. Demographic and baseline characteristics are shown in Table 1.

**FVIII+/vWF+ Compared With FVIII−/vWF−**

Table 2 demonstrates in-hospital events and discharge outcomes for the groups. After adjusting for age, NIHSS, and glucose, FVIII+/vWF+ patients were at increased odds of having poor functional outcome (odds ratio [OR]=2.87; 95% confidence interval [CI], 1.17–7.06; P=0.021). After additional adjustment for tissue-type plasminogen activator, patients with FVIII+/vWF+ were more likely to experience inpatient complications (OR=8.6; 95% CI, 1.57–46.85; P=0.013), neuroworsening (OR=3.21; 95% CI, 1.18–8.72; P=0.022), and recurrent thrombotic events (OR=4.21; 95% CI, 1.57–11.28; P=0.004).

**FVIII−/vWF+ Compared With FVIII−/vWF−**

Patients with FVIII−/vWF+ were at increased likelihood of experiencing poor functional outcome (OR=3.43; 95% CI, 1.04–11.34; P=0.043) and unfavorable discharge disposition (OR=3.46; 95% CI, 1.00–11.92; P=0.049) than those in the FVIII−/vWF− group after adjusting for age, NIHSS at baseline, baseline glucose level, and tissue-type plasminogen activator.

**Discussion**

Our study is the first to examine the relationship between FVIII and vWF with respect to patient characteristics and outcomes in the setting of AIS. Almost half of our sample had either elevated FVIII or vWF, and over one third had concurrent elevation, suggesting that elevation in these factors is not rare among patients with AIS and merits exploration.

Groups of patients with FVIII+, regardless of vWF, had elevated erythrocyte sedimentation rate and C-reactive protein compared with those in the FVIII−/vWF− group, suggesting that FVIII may be driving this association and supporting elevation in FVIII as an acute phase response. Given that the FVIII+/vWF+ group was not associated with higher inflammatory markers, but was associated with worse outcomes, the results suggest that vWF elevation is clinically relevant, independent of inflammation.

Patients in the FVIII+/vWF+ group experienced recurrent thrombotic events and neuroworsening with significantly greater frequency. Isolated FVIII+ is associated with patient baseline characteristics and may be related to stroke onset and the acute phase of stroke. Groups of patients with vWF+, regardless of FVIII, had higher median discharge modified Rankin Scale scores. Taken together, our results suggest that elevation of FVIII and vWF relate to different stages of AIS progression. Combined elevation of FVIII and vWF seems to be related to in-hospital events, suggesting a cooperative effect on AIS progression.

This study is limited by single measurement of FVIII/vWF, cross-sectional design, and relatively small sample size. Testing of FVIII/vWF was not random or universal, which likely results in selection bias and limits generalizability. Our results require validation in a prospective study using serial measurements to determine whether concurrent FVIII/vWF elevation is related exclusively to the acute phase of stroke or is more broadly related to both stroke risk and recovery.

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**Disclosures**

None.

**References**

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