Excess Factor VIII: A Common Cause of Hypercoagulability

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Background: Elevations of coagulation factor VIII have recently been described in significant numbers of patients with venous thromboembolism (VTE) previously thought to have had an “idiopathic” event. Three patients from a family practice are presented with recurrent VTE and increased factor VIII levels.

Method: The case histories and results of laboratory tests were reviewed.

Results: The 3 patients had no other clear coagulopathy. In 2 of the 3, the increase was confirmed with a second reading.

Conclusions: Factor VIII assay should be considered in the work-up of idiopathic, recurrent VTE. Long-term anticoagulation may be appropriate in this setting. (J Am Board Fam Pract 2005;18:147–9.)

Venous thromboembolism (VTE) is seen frequently in primary care. With the advent of sophisticated laboratory testing, at least half of previously idiopathic cases can be found to have a coagulation disorder. Although the heritable factor V Leiden mutation has been believed to be the most common of these (5% of the white population is heterozygous for the disorder), increased activity of factor VIII has recently emerged as a relatively common identifiable cause of hypercoagulability. In 1995, Koster et al studied 301 VTE patients without cancer and matched control subjects and found a dose-response relationship between factor VIII concentration and risk of thrombosis; subjects with factor VIII activity above 150% (150 IU/dL) represented 25% of the sample and had an adjusted odds ratio for VTE of 4.8. Kraaijenhagen et al found a 33% prevalence of factor VIII activity above 175% (the 90th percentile) in recurrent VTE cases, and concluded that such elevated plasma levels were a significant, prevalent, independent, and dose-related risk factor. Kyrle et al followed patients with a first episode of VTE after anticoagulants had been discontinued and found patients above the 90th percentile for plasma factor VIII levels had a 6.7-fold relative risk of recurrence compared with those with lower levels. Elevated factor VIII levels have been found to persist over time and to be independent of the acute phase response. (The studies above nevertheless re-measured factor VIII several months after the VTE event.)

This is a report of 3 cases of thromboembolism not associated with conventional risk factors (trauma, cancer, or immobility). The patients were found to have elevated factor VIII activity without other evidence of a hypercoagulable state.

Case 1

A 40-year-old man with recurrent attacks of shortness of breath and syncope was diagnosed with multiple distal pulmonary emboli by computed tomographic angiography. There was neither a past history nor a family history of thromboembolic disease. He was a smoker and took paroxetine and trazodone. Venous duplex scans of both legs were negative for deep vein thrombosis (DVT). Results of laboratory tests are shown in Table 1. Lupus anticoagulant screen ratio was initially weakly positive, but the results of a confirmatory test (screen/confirm ratio) were negative, and phospholipid dependence could not be confirmed. Anticardiolipin IgM at 13 fell into the laboratory’s “indeterminate” range (12.5–20 MPL units; 1 MPL unit = 1 μg of affinity-purified IgM anti-cardiolipin antibodies from an original index serum sample), but low-level IgM antibodies occur with other conditions and are not associated with thromboembolism. All other coagulation factors were unremarkable, except for a markedly elevated factor VIII activity. The patient was on heparin and warfarin at this time. A second factor VIII assay, which was performed on an outpatient basis a year later, by a different lab, was normal at 126%.
Case 2
A 63-year-old woman was admitted for a pulmonary embolism; on duplex scanning of the lower extremities, 2 clots were also found in the left leg. She had a history of one miscarriage and 4 live births. Her brother had a myocardial infarction at age 39, and her father died of a myocardial infarction at age 63. She also had chronic obstructive pulmonary disease and hypertension. She had quit smoking 4 years before presentation. Results of laboratory tests are summarized in Table 1. The factor VIII elevations were the most striking abnormality. These were found several months after the embolism as part of a coagulopathy work-up; the 2 levels were taken 11 days apart to confirm persistent elevation. The patient was on warfarin at the times of testing.

Case 3
A 45-year-old man was admitted for a symptomatic (painful) left leg DVT. He had had a DVT of the same leg at age 16. He was a smoker. His history included schizophrenia and his medications were omeprazole, benzotropine, divalproex, and olanzapine. There was no family history of thromboembolic phenomena. Results of laboratory tests are summarized in Table 1. Lupus anticoagulant screen ratio, initially increased, could not be confirmed with a mixing study (screen/confirm ratio was negative). Anticardiolipin IgG fell into the laboratory’s “indeterminate” range and would not meet the criteria for antiphospholipid antibody syndrome. A factor VIII level that had been obtained on an outpatient basis about 1 year before the hospitalization, in the course of a coagulopathy workup, was elevated at 326%. During the admission, it was 247%. The patient was on enoxaparin at the times of testing.

Discussion
Factor VIII levels above normal (>150 IU/dL) can be found in 11% of the general adult population. It is also a significant VTE risk factor for children. It has only recently been appreciated that this entity may account for a significant proportion of idiopathic hypercoagulable states. In clinical practice, most people being worked up for recur-
rent VTE will be taking anticoagulation agents, but this should not affect the results of factor VIII assays. (The Stony Brook University laboratory uses a partial thromboplastin-based assay that is unaffected by anticoagulants that patients may be taking.) Patients 2 and 3, above, had persistent elevations in factor VIII, with at least one result separated in time from the acute VTE event. This could not be demonstrated with patient 1, although the second assay was done at a different lab.

**Conclusion**

Factor VIII excess is a recently described, apparently common, and under-recognized cause of VTE. Some reviews\(^1,13\) of hypercoagulability do not mention factor VIII excess. It persists over time, may be genetic,\(^4,8\) and is associated with about a 6-fold increase in VTE events.\(^3,5\) In one study, patients with levels above the 90th percentile (\(>234 \text{ IU/dL}\)) had a 37% likelihood of recurrence of a thromboembolic event within 2 years.\(^5\) Our understanding of this entity is evolving; guidelines for treatment and for frequency and methodology of testing do not yet exist. It does seem that patients with recurrent or unusual VTE who have persistent elevations of factor VIII activity (\(>150\%\)) may be candidates for long-term prophylaxis with warfarin.

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**References**