Elevated Factor VIII: An Unfamiliar Risk Factor for Cerebral Venous Thrombosis

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An elevated factor VIII level has been shown to be an independent risk factor for venous thrombosis. However, physicians screen for this factor far less frequently than they screen for other coagulopathies. The causes of increased factor VIII levels are likely a combination of genetic and acquired variables. The authors describe a case of a healthy 48-year-old woman found to have a cerebral venous thrombosis, with her only identifiable risk factor being an elevated factor VIII level.

Report of Case

A 48-year-old African American woman with a past medical history of anxiety presented to the emergency room with an acute change in mental status. The patient’s husband reported that she had been in her usual state of health with the exception of a headache the day before presentation. On the morning of admission, the patient went grocery shopping and on her return appeared confused and disoriented. The patient’s husband also reported that her gait was unsteady and that she had an episode of urinary incontinence.

The patient was not taking any medications or supplements and consumed 6 beers daily. Family history included breast cancer in her mother and prostate cancer in her father. On physical examination, the patient was afebrile and hemodynamically stable with a Glasgow Coma Scale score of 11. During neurologic examination, the patient was combative, spoke inappropriately, and was indifferent to her surroundings. However, she had equally round and reactive pupils and full range of motion in all 4 extremities.

Laboratory findings were normal. Results of a urinary drug screen and noncontrast computed tomography of the brain performed on the day of admission were unremarkable. A lumbar puncture was performed; cerebral spinal fluid testing was negative for white blood cells and revealed a protein level of 75 mg/dL and glucose level of 86 mg/dL. The patient was given empiric intravenous thiamine hydrochloride and acyclovir sodium for Wernicke encephalopathy and herpes encephalitis. On hospital day 2, magnetic resonance imaging of the brain revealed new hydrocephalus, and an electroencephalogram showed changes consistent with diffuse encephalopathy of nonspecific origin. Results of contrast-enhanced computed tomography of the chest, abdomen, and pelvis were unremarkable. On hospital day 4, cerebrospinal fluid testing was negative for bacterial, fungal, and acid fast cultures and cryptococcal antigens, and the patient was given methylprednisolone (125 mg intravenously). On day 5, cerebrospinal fluid testing for herpes simplex virus returned negative results and acyclovir was discontinued. On day 6, the patient was showing little improvement, so magnetic resonance angiography/venography was performed. This imaging revealed thromboses of the paired deep internal cerebral veins, the Galen vein, and the straight sinus (Figure).

After the diagnosis of a cerebral vein thrombosis, warfarin therapy (7.5 mg daily) was initiated. Before diagnosis, a comprehensive panel was drawn for coagulopathies and vasculitides. These findings were negative for antiphospholipid antibody, lupus anticoagulant, factor V Leiden, factor II gene mutation, β2 glycoprotein 1 antibody, antinuclear antibody, cryoglobulinemia, antineutrophil cytoplasmic antibody–associated vasculitis, and human immunodeficiency virus. The patient’s protein C and
protein S activity, protein electrophoresis, homocysteine levels, and thyroid stimulating hormone levels were normal. The only remarkable laboratory value was an elevated factor VIII assay at a level of 399% (reference range, 75% to 160%).

The patient remained in the hospital for 34 days. Her mental status improved substantially, and, at the time of discharge, she was oriented with an appropriate affect and able to answer questions properly. She was instructed to remain on warfarin (7.5 mg daily) indefinitely. The patient was followed up 2 weeks after discharge, at which time her husband reported that her mental status had returned to baseline (ie, mental status prior to the encephalopathic event).

Comment
Elevations in factor VIII levels are thought to be an independent risk factor for venous thrombosis. Levels above 150% have been shown to be associated with a fivefold increased risk of venous thrombosis. Additionally, patients with a factor VIII level above the 90th percentile have been shown to have a 37% risk of recurrence at 2 years, suggesting that factor VIII hyperactivity may also be an independent risk factor for recurrent venous thrombosis. To our knowledge, there have been only a few cases of cerebral vein thrombosis in the setting of elevated factor VIII levels. However, several studies have suggested that this derangement may account for a large number of these events. Cakmak et al found that an elevated factor VIII level was the most common coagulopathy, occurring in 6 of 12 patients with cerebral vein thrombosis.

The exact basis for increases in factor VIII is not completely understood, but it is likely a combination of genetic and acquired variables. Genetic factors such as increased von Willebrand factor levels and non-O blood groups have been associated with elevated factor VIII levels. An increase in factor VIII has been particularly noted to be more common in the African American population. Patel et al found levels above the 90th percentile in 34 of 100 black patients with a history of venous thrombosis, compared with 10% of black control patients. Additionally, the odds ratio for the risk of venous thrombosis for black patients with elevated factor VIII levels in this study was reported to exceed those reported for white patients. Acquired factors, such as increased body mass index, hyperglycemia, hypertriglyceridemia, pregnancy, surgery, chronic inflammation, malignancy, liver disease, hyperthyroidism, intravascular hemolysis, and renal disease have been linked to increased levels as well.

Several studies support the belief that an increase in factor VIII is the cause of thrombosis rather than the consequence. The risk for recurrent thrombosis has been shown to be as high as 37% in patients with high factor VIII levels, a risk that may warrant lifelong anticoagulation. O'Donnell et al showed that high factor VIII levels persist over time in patients with a cerebral vein thrombosis. Furthermore, Kyrle et al and Kamp- huisen et al showed there is not a statistically significant relationship between plasma levels of factor VIII and C-reactive protein, suggesting that this factor is not an acute phase reactant.

Conclusion
Patients who experience a thrombotic event should be evaluated for factor VIII hyperactivity in addition to other commonly screened genetic coagulopathies.

References