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A rare manifestation of a rare disorder: Acquired Hemophilia A presenting as intracerebral hemorrhage

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Abstract

Acquired Hemophilia A (AHA) is a rare coagulopathy caused by autoantibodies against Factor VIII, disrupting the intrinsic clotting cascade and leading to life-threatening bleeding. Intracranial hemorrhage due to AHA is a rare manifestation of this disorder, but recognition is important because treatment requires both replacement of coagulation factors as well as immunosuppression. We report a case of basal ganglia hemorrhage due to AHA that underscores the importance of early detection and the possibility of a favorable outcome when recognized and treated expeditiously.

Keywords

acquired hemophilia A; activated partial thromboplastin time (aPTT); factor VIII; coagulopathy

Abbreviations

CT: Computerized tomography; MRI: Magnetic resonance imaging; aPTT: activated partial thromboplastin time; PT: Prothrombin time; INR: International normalized ratio; AHA: Acquired hemophilia A; ICH: Intracranial hemorrhage

Case Presentation

A 73-year-old man with hypertension presented with a severe retro-orbital headache and confusion. On arrival, he was normotensive and mildly drowsy with a left hemiparesis and dysarthria. A non-contrast brain computerized tomography scan (CT) demonstrated a 5 cc right basal ganglia hemorrhage with 5 mm midline shift and extensive intraventricular hemorrhage (Figure 1). Hemoglobin was 8.7 g/dL, hematocrit was 28.6%, and platelet count was 392,000 platelets/mL. Prothrombin time (PT) was 12.4 seconds (normal: 11-13.5) and international normalized ratio (INR) was 1.1 (normal: 0.8-1.1). Anti-Xa level was undetectable. Activated partial thromboplastin time (aPTT) was markedly elevated at 101 seconds. The patient did not take anticoagulants and had no prior history of coagulopathy.

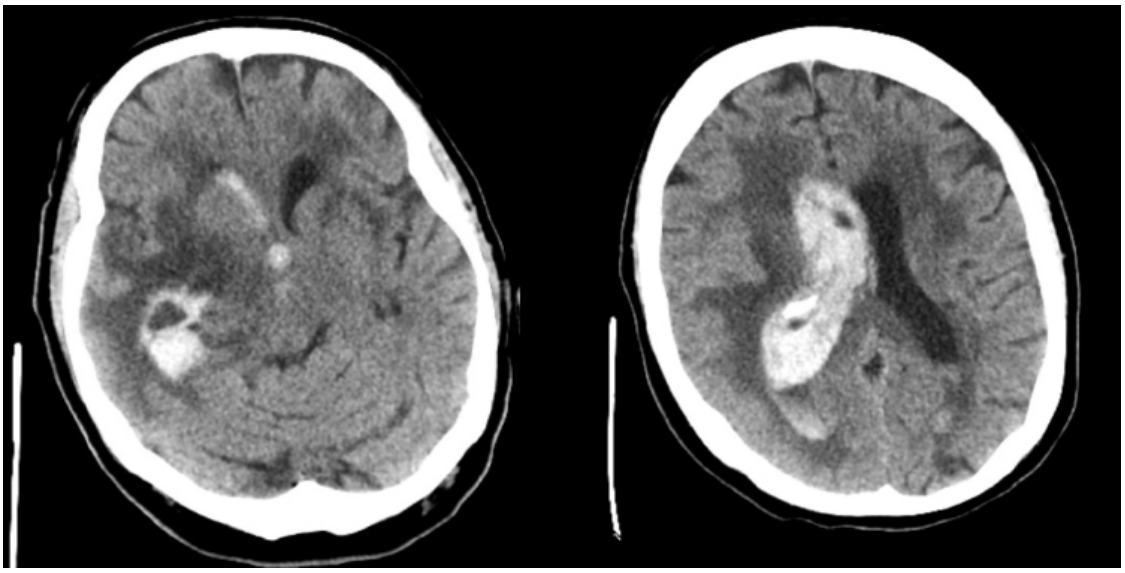

Figure 1: Demonstrates right basal ganglia hemorrhage with intraventricular extension and mild obstructive hydrocephalus

Further labwork revealed undetectable Factor VIII activity (normal: 50-150%), negative testing for lupus anticoagulant and normal Factor XI and IX activity. Subsequent testing for Factor VIII inhibitor was markedly elevated at >70 Bethesda units (normal: 0) consistent with acquired hemophilia A (AHA).

The patient was admitted to the neurocritical care unit, and immediately given a dose of activated Factor VII (90 mcg/kg), while recombinant Factor VIII was obtained and sub-sequently initiated. Prednisone and cyclophosphamide were administered. Neurologic examination and repeat head CTs remained unchanged. He required several days of Factor VIII, with resultant response in Factor VIII activity from undetectable on admission to 172% at discharge.He was discharged on cyclophosphamide and prednisone, which were tapered off with sustained normalization of his Factor VIII levels. On neurologic follow-up, the patient was ambulating with a cane and noted mild cognitive impairment, but was able to return to all of his pre-morbid activities with the exception of driving.

Discussion

Acquired Hemophilia A (AHA) is a rare disease with an incidence of 1 per every 1.5 million persons [1]; it is caused by autoantibodies against Factor VIII. It is rare in children, and the median age of presentation is 73 years [2]. According to registry data, there is a slightly higher incidence in men as compared to women [2], although there is a subset of women who develop AHA while postpartum.

Presentation and Pathophysiology

The classic presentation is mucosal or subcutaneous bleeding in a patient with no prior personal or family history of coagulopathy or excessive bleeding; in contrast to congenital hemophilia A, hemarthroses are uncommon [3, 4]. Intracerebral bleeding has been previously described in the literature, though it is rare [5-10] and typically occurs in the setting of trauma or surgery.

AHA can be idiopathic, such as the case with our patient, or it can be associated with an underly-

ing secondary condition such as collagen vascular disease, malignancy, or as an idiosyncratic reaction to medication [11]. More recently, nivolumab, a checkpoint inhibitor used in treating certain cancers, has been reported to be associated with AHA [12]. AHA occurs when antigen presenting cells take up Factor VIII and interact with B cells, causing production of IgG autoantibodies against Factor VIII [3]. Normally, Factor VIII interacts with thrombin to bind to Factor IX, leading to thrombin activation and commencement of the intrinsic pathway; in the absence of factor VIII, the coagulation cascade is severely impaired leading to an increased risk of bleeding (Figure 2). Laboratory findings are crucial for diagnosis. Often the first clue is a significantly prolonged aPTT which does not correct with mixing studies, indicating the presence of an inhibitor [3]. INR may be normal or mildly prolonged. Subsequently, Factor VIII activity will be undetectable; positive Factor VIII inhibitor confirms the diagnosis. Notably, factor VIII levels do not predict severity of bleeding [11]. Interestingly, about 15% of otherwise normal healthy individuals who have low titers of factor VIII inhibitory antibodies in the absence of any clinical manifestations [13]; the significance of this finding is not known.

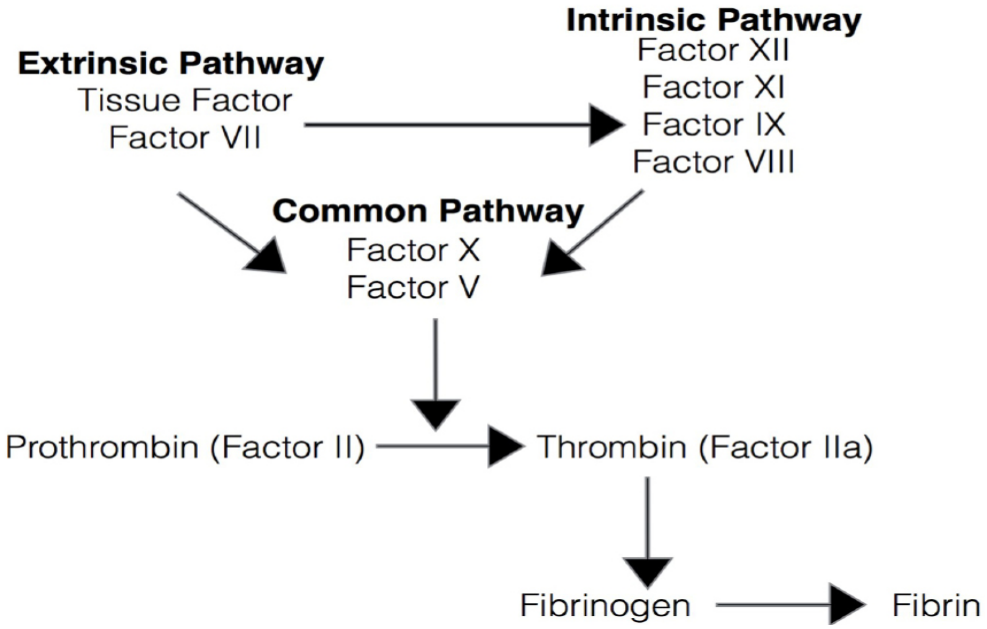

Figure 2: Demonstrates the coagulation cascade

Treatment

Treatment of AHA consists of immediate reversal of the coagulopathy to halt bleeding, and prolonged immunosuppression to eradicate the inhibitor and restore normal function to the coagulation cascade. Coagulopathy in patients with AHA is reversed by administering coagulation factors. Factor VIII is available, however, high inhibitor titers, exogenously administered Factor VIII may be insufficient, and either prothrombin complex concentrate or Factor VII may be necessary [3]. The current recommendations from the Italian Association of Hemophilia Centers (AICE) are that bypassing agents are considered first line for reversal of coagulopathy [14]. One retrospective study showed that bypassing agents are much more efficacious for controlling bleeding, with 91.8% of patients achieving bleeding control with bypassing agents versus 69.6% with replacement therapy [15]. However, other authors report that porcine Factor

VIII may also be effective, as the structure of the porcine protein varies from human Factor VIII such that it may not be recognized by autoantibodies [10]. The most feared complication of coagulation factor administration is thrombosis, which has been reported to be approximately 2.9% in patients given recombinant Factor VIIa [16]. In some cases, desmopressin may be used; however, for severe bleeding, replacement of coagulation factors is required. Transexamic acid can also be considered in some cases of mucosal bleeding, except in cases of renal bleeding where it is contraindicated [14]. The AICE recommendations also state that patients with underlying conditions such as autoimmune disease or malignancy should be treated for their primary etiology, analogous to the importance of treating the underlying cancer in other types of paraneoplastic syndrome. Immunosuppression with a combination of steroids and cyclophosphamide is successful in most patients [17]; steroids either alone or in combination with cyclophosphamide are currently considered first-line treatment [14]. However, cyclophosphamide is contraindicated in pregnancy and is associated with a significant risk of side effects, including neutropenia, and so discretion is required. In refractory cases, rituxumab intravenous immunoglobulin, and plasma exchange have also been tried [3,14].

Neurologic complications

Neurologic complications of AHA are not common, but are potentially devastating. Intracranial hemorrhage, such as the presentation in our patient, is rare in AHA; a review of the literature revealed 11 case reports (Table 1). In some cases, surgery or trauma precipitated the hemorrhage, but in others, the bleeding occurred spontaneously. Case series have demonstrated an incidence of AHA-related ICH in approximately 1.1-4.1% of patients [2,18,19]. Notably, ischemic stroke can occur as a complication of AHA as well, by way of border zone infarction in the context of severe systemic bleeding [20] or thrombotic stroke after factor replacement [21-23]. Clinicians therefore must be vigilant to the possibility of both ischemic and hemorrhagic stroke in these patients.

Prognosis

In general, 70-90% of patients with AHA present with life-threatening bleeding, with a 5-10% case fatality rate, most commonly from bleeding or sepsis [17]. However, if patients survive the acute hemorrhage, 72-78% achieve remission with treatment [10]. A third of patients with low inhibitor titers of less than 5 BU clear the antibody on their own without immune suppression [13]. Of note, 20% of patients can experience recurrence, so close clinical and laboratory monitoring is imperative, even when patients achieve remission [1,14]. In the case reports of patients with intracranial hemorrhage, 4 of 11 patients died, though a confounding factor may have been neurosurgical evacuation with postoperative hematoma expansion in three cases. Due to the rarity of this presentation, it is unclear if ICH confers a higher mortality than other types of bleeding in AHA.

Table 1: Prior cases reported of ICH in the setting of Factor VIII deficiency

Author (Year)	Patient Presentation	Location of Hemorrhage	Labs on Presentation	Treatment and Outcome
Akamatsu (2017)	Epistaxis, wound bleeding, and intracranial hemorrhage after delayed cranioplasty post-aneurysm clipping	Hemorrhagic transformation of surgically disrupted parenchyma	Prolonged aPTT Positive Factor VIII inhibitor	4 days of fresh frozen plasma transfusions. Recovered with lab normalization by 5 weeks without immunosuppression
Araf (2013)	Headache and left sided weakness; no prior history of surgical manipulation	Right thalamus	aPTT = 53 seconds	Prednisolone; patient survived but functional outcome not reported
Bonnaud (2003)	Headache and drowsiness with no history of trauma	Right holohemispheric subdural hematoma	prolonged PTT (exact value not reported but 3.45 normal) factor VIII activity = 1% factor VIII inhibitor = 4.4 BU	Prednisone, cyclophosphamide, recombinant factor VII, IVIG. Clinical status stabilized with immunosuppression
Marquardt (2006)	Subcutaneous hematomas and left hemiparesis	Intracerebral	Factor VIII inhibitor positive	Factor VIIa, open hematoma evacuation, cortisone, cyclophosphamide. Patient developed recurrence of hemorrhage and died due to brainstem compression
Mashiko (2009)	Found in comatose state	Left subdural hematoma; postoperatively multiple intraparenchymal hematomas including thalamus, temporal lobe	aPTT = 77 seconds	Initially treated with resection of subdural hematoma with FFP; then Factor VIII and Factor IX. Patient died after multifocal repeat hemorrhages
Micic (2011)	Headache, dysarthria, and confusion	Right cerebellum	aPTT = 53.4 sec Factor VIII activity = 13% Factor VIII inhibitor = 1.7	Emergent surgery prior to discovery of Factor VIII inhibitor. Patient developed exam decline with repeat scans showing new multifocal hematomas; care withdrawn after family discussion; died
Mikami (2005)	Oozing from the hematoma site in a man who underwent surgery for a ruptured aneurysm with hematoma	Right frontal epidural hematoma	normal preoperative coagulation parameters (not specified) postoperative: aPTT of 84.4 s factor VIII level 6%	Treated with prednisolone; had recurrent subcutaneous bleeding and intramuscular bleeding but no further severe bleeds. Transitioned to cyclosporine and weaned off steroids with no further bleeding events for five years.
Sehara (2015)	Left hemiparesis after a minor trauma (fall from bed)	Right holohemispheric subdural hematoma	aPTT 104.2 s Factor VIII 4% Factor VIII inhibitor 3 BU	Treated with fresh frozen plasma; immunosuppression with methylprednisolone followed by oral prednisone.

Our case (2018)	Headache and left hemiparesis	Right basal ganglia with intraventricular extension	aPTT = 101 Factor VIII activity = <1% Factor VIII inhibitor = >70.0 BU	One dose of Factor VII followed by several doses of Factor VIII. Prednisone and cyclophosphamide. Eventual normalization of coagulation parameters except mildly prolonged PTT, no further bleeding events
Tsuyama (2016)	Leg swelling due to intramuscular hematoma, and gait disturbance due to hemorrhage; no trauma or surgery	Right thalamus	aPTT= 34.7 Factor VIII activity = 22.2% Factor VIII antibody = 1	Treated with prednisone with resultant normalization of coagulation parameters
Wool (2017)	Left sided weakness and occipital headache	Right thalamus	aPTT= 76.9 seconds Factor VIII activity = 4%	Prothrombin concentrate, recombinant Factor VIII, Factor VII, dexamethasone, therapeutic plasma exchange. Developed pulmonary embolism, followed by cardiogenic shock, and died in hospital

Conclusion

AHA is a rare etiology of ICH requiring prompt identification and treatment; it can occur in patients with no prior history of bleeding and as the first presentation of AHA. An isolated aPTT can occur in the presence of a normal PT and INR, illustrating the importance of aPTT in the laboratory evaluation of patients with ICH. If diagnosed and treated quickly, patients can have a favorable outcome, as illustrated in our patient. This case illustrates the importance of further workup when aPTT is elevated without explanation.

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