Thromboelastometry as a Comprehensive Assessment of Hypercoagulation After Aneurysmal Subarachnoid Hemorrhage: A Case Report and Literature Review

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Abstract Subarachnoid hemorrhage after cerebral aneurysm rupture (aSAH) leads to delayed cerebral ischemia (DCI) in 25–35% of surviving patients. It is believed that DCI has a multifactorial etiology, including vasospasm. Furthermore, aSAH is associated with the development of hypercoagulation and microthrombosis; thus, its pharmacological correction may help to prevent DCI. We encountered a case where hypercoagulation was detected using rotational thromboelastometry (ROTEM), although the standard coagulation test results were within the normal ranges. Based on reviews of viscoelastic tests in cases of aSAH, ROTEM could be more sensitive to hypercoagulation after aSAH, compared to standard coagulation testing.

Keywords Subarachnoid hemorrhage · Microthrombosis Delayed cerebral ischemia · Secondary brain injury

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is an acute cerebrovascular disease associated with high levels of mortality and disability [1]. Delayed cerebral ischemia (DCI) remains one of the main causes of poor neurological outcome after aSAH [2]. The mechanisms underlying the formation of DCI are incompletely understood. The historical assumption was that large-vessel cerebral vasospasm was the only cause of DCI. However, most of patients with aSAH develop angiographic vasospasm, but only ≥30% develop DCI [3]. Recent evidence indicates that other pathological mechanisms apart from vasospasm are involved [4]. For example, the coagulation system is activated early after the initial SAH, and these hypercoagulation changes lead to microthrombosis, which is considered one of the main pathophysiological mechanisms leading to DCI [5]. Adequate diagnosis of hypercoagulation and early initiation of prophylaxis and treatment may help prevent DCI (Fig. 1).

Case Report

A 52-year-old woman was admitted after rupture of an anterior communicating artery aneurysm, which led to intracerebral and intraventricular hemorrhages (Fisher IV) (Fig. 1). The patient was in stupor (Glasgow coma scale score, 10 points) with left-side hemiparesis, severe headache, and nuchal rigidity (Hunt-Hess 4 points). The patient was followed up in the neurocritical care department with a standard local protocol of care for acute period of aSAH, including early performed neurosurgery (aneurysm occlusion), intensive care with invasive hemodynamic monitoring, and management of intracranial complications. After aneurysm clipping, we evaluated hemostasis based on standard coagulation tests (Table 1) and rotation thromboelastometry (ROTEM) parameters (Table 2).

Blood samples were obtained via direct peripheral venipuncture after a tourniquet was placed for ≤30 s. Appropriate volumes were collected in vacuum tubes containing sodium citrate, and the first tube was not included in the coagulation testing. All coagulation tests were performed within 10 min after blood collection. ROTEM was performed using whole blood that was incubated at 37 °C in a heated cup. A pin in the cup was connected to an optical detector system, and the cup and pin were oscillated relative to each other. The forming clot impedes the pin's rotation, and the extrinsic coagulation pathway (EXTEM assay) and intrinsic coagulation cascade (INTEM assay) were evaluated. The influence of fibrinogen on clot firmness was estimated using the platelet-inactivating FIBTEM assay [6]. The following ROTEM parameters were

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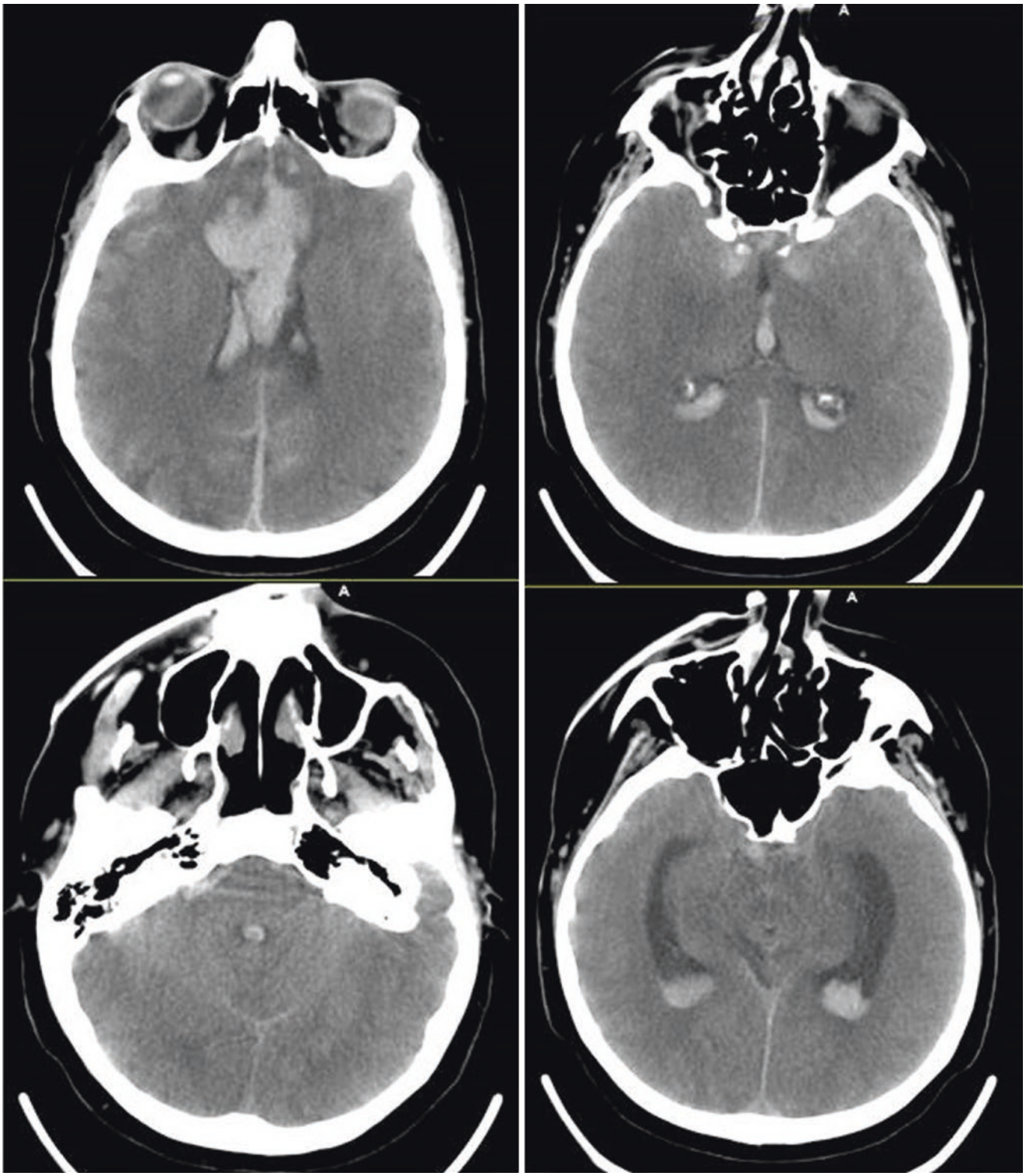

Fig. 1 Computed tomography scan upon admission

analyzed: (1) clotting times (CT, s), initiation of clotting, thrombin generation, and start of fibrinogen polymerization; (2) clot formation time (CFT, s) and α, estimation of clot growth kinetic by fibrin polymerization, platelets, and factor XIII; (3) clot strength based on oscillation amplitude at fixed times (A10–A20); and (4) maximum clot firmness (MCF). The standard coagulation tests included activated partial thromboplastin time (APTT), international normalized ratio (INR), fibrinogen level, and inhibition of factor X (anti-FXa assay). These tests were performed using ACL 9000 analyzer.

All standard coagulation test results were considered normal, although thromboelastometry revealed hypercoagula-

tion based on increased clot strength (elevated MCF values in the INTEM, EXTEM, and FIBTEM assays) on the second day after the aSAH. The patient also had clinical signs of hypercoagulability, such as preliminary thrombosis in the veins of the lower extremities. Infections of the central nervous system, blood, and urinary tract were excluded as causes of the hypercoagulation, as well as pneumonia and diabetes. Anticoagulation therapy was initiated with low-molecular-weight heparins (LMWH) and maintained within the prophylactic range using the anti-FXa assay (0.32). The next day, before the LMWH treatment, a dynamic evaluation of the hemostasis was performed using ROTEM, which revealed persistent hypercoagulability. Thus, a therapeutic LMWH dose was administered (0.6). The patient was discharged after 36 days, with clear consciousness and no signs of hypercoagulation (complete regression of venous thrombosis and the absence of ischemic foci on the brain CT scan).

Table 1 Serum lab values at serial time points after aSAH

	Normal range	PBD 1	PBD 2	PBD 3	PBD 4	PBD 5
APTT	25.4–36.9 s	27.0	25.5	26.4	26.2	25.7
INR	Below 1.1	0.96	1.10	1.00	1.00	0.98
Fibrinogen	1.7–4.4 mg/dL	3.5	4.0	3.3	3.6	3.8
D-dimer	Below 550 ng/mL	618	620	627	631	630
Platelet count	150–450 10^3/µL	243	237	226	240	200

PBD post bleed day; *APTT* activated partial thromboplastin time; *INR* international normalized ratio

Table 2 Parameters of ROTEM at serial time points after aSAH

	Normal range	PBD 1	PBD 2	PBD 3	PBD 4	PBD 5
EXTEM						
CT	38–79	53	68	77	72	57
CFT	34–159	57	70	85	73	99
α	63–83	79	76	73	76	71
A10	43–65	65	65	61	67	59
A20	50–71	70	76	72	71	66
MCF	50–72	71	76	74	71	68
INTEM						
CT	100–240	195	197	195	186	173
CFT	30–110	56	58	57	57	76
α	70–83	78	78	75	79	75
A10	44–66	64	65	60	67	56
A20	50–71	70	78	72	71	62
MCF	50–72	70	78	74	71	62
FIBTEM						
CT	38–62	54	59	62	62	51
α	N/A	79	78	75	72	73
A10	7–23	22	**27**	**24**	22	21
A20	8–24	23	**28**	**26**	22	22
MCF	9–25	23	**28**	**27**	23	22

Literature Review

Over the last years, vasospasm has been identified as the main pathophysiological mechanism contributing to DCI. However, recent studies suggest a multifactorial etiology of DCI, including microvascular dysfunction and microthrombi formation [4, 5, 7, 8].

Tissue factor (TF) is expressed by various cells within the vessel wall and surrounding blood vessels; thus, the endothelium physically separates this potent "activator" of hemostasis from the blood flow [9–12]. High levels of TF are detected in the brain, lungs, heart, kidneys, and placenta, while low levels are usually detected in the liver, spleen, skeletal muscle, and thymus [9]. High TF levels in the brain help to protect against intracranial hemorrhage, and damage to cerebral vessels can lead to hypercoagulation and thrombosis [4, 12].

The appearance of procoagulant activity precedes DCI [13], and Stein et al. [14] have reported that microthrombosis preceded DCI in various brain structures (e.g., cingulate, hippocampal, and insular areas) of 29 patients after fatal aSAH. For example, significantly more microthrombi were detected in patients with signs of DCI, compared to patients without ischemic lesions (10.0/cm^2 vs. 2.8/cm^2). Sehba et al. [15] also detected increased platelet aggregation in cerebral vessels within 10 min after rupture in animal models of aSAH. Juvela et al. [16] evaluated platelet aggregation and release of thromboxane B2 in 52 patients with aSAH and reported that increased platelet activity and thromboxane release were associated with DCI development. Furthermore, the highest values for thromboxane release were observed in patients with clinical and radiological signs of DCI. Another possible mechanism for hypercoagulation after aSAH involves the vasopressin receptor V1a, which is broadly dispersed throughout the brain (e.g., on the surface of endothelial cells) [17], as the interaction between vasopressin and the V1a receptor promotes platelet aggregation and vasoconstriction [18]. Thus, Liu et al. [19] studied the dynamics of vasopressin V1a receptor expression and its effect on platelet aggregation in experimental aSAH models and found that vasopressin levels rapidly increased during the first 6–24 h after hemorrhage. The peak expression of GPIIb/IIIa integrin responsible for platelet aggregation was located in the cortex and hippocampus, and was co-localized with vasopressin, which led the authors to conclude that high plasma levels of vasopressin were correlated with secondary brain damage after experimental aSAH [20]. Foreman et al. [21] have also reported that nosocomial infections were associated with DCI among 156 patients with aSAH, which they attributed to

a systematic inflammatory response leading to thrombosis and subsequently ischemia. Ettinger [22] reported that, among patients with aSAH, significantly elevated fibrinogen levels were associated with an increased risk of mortality. Other researchers [23] have also indicated that elevated levels of fibrinogen, D-dimers, and thrombin-antithrombin complex may be predictors of DCI after aSAH.

A search of the PubMed database using "thromboelastography" and "subarachnoid hemorrhage" only returns two studies that examined thromboelastography (TEG) in cases of aSAH. Ramchand et al. [24] evaluated 22 patients with moderate-to-severe SAH based on several TEG parameters, complete blood count, fibrinogen, C-reactive protein, and D-dimers at 1–10 days after hemorrhage and reported that TEG-detected hypercoagulation was associated with poor outcomes. Furthermore, they reported that the associations between several TEG parameters and the outcomes were stronger than the associations with traditional biomarkers. Frontera et al. [25] also analyzed platelet function in 106 patients with aSAH using TEG, as well as C-reactive protein dynamics. In that study, patients with severe early brain injury after aSAH (Hunt-Hess grade 4–5) had significantly increased levels of platelet activation and C-reactive protein compared to the control group, which were associated with poor 3-month functional outcomes.

Although aSAH is associated with the development of hypercoagulation and formation of microthrombosis, which may lead to DCI, the pathophysiological mechanisms underlying aSAH-related hypercoagulation are incompletely understood. Several studies have suggested that the relationship is driven by platelet hyperaggregability, while others have suggested that high brain levels of TF can predispose the patient to hypercoagulation.

Discussion

In the present case, we examined whole-blood samples using ROTEM, which revealed elevated clot strength (increased MCF during the INTEM, EXTEM, and FIBTEM assays), although normal results were observed during standard coagulation testing. This may because the most widely used screening tests (INR, APTT, and fibrinogen level) are performed using plasma, which may obscure information regarding interactions between coagulation factors and phospholipid surfaces, provide limited information regarding clot stability, and fail to detect minor shifts of hemostasis [12]. Thus, we believe that viscoelastic testing using whole blood is necessary during the acute period of aSAH. In this context, point-of-care viscoelastic testing using TEG and ROTEM provides more complete information regarding hemostasis by simultaneously measuring coagulation, platelet function, and fibrinolysis [6]. Moreover, the FIBTEM assay abolishes platelet function using cytochalasin D (an inhibitor of actin polymerization) and generates data specifically regarding fibrinogen. This crucial differentiation between the contributions of platelets and fibrin to clot strength can facilitate customized prophylaxis and microthrombosis treatment. Previous studies have suggested using the maximum amplitude from TEG, although this parameter does not distinguish fibrin and platelet bonding via GPIIb/IIIa and is strongly correlated with platelet function, which precludes a pathophysiological customized treatment. As our patient exhibited clinical and laboratory signs of hypercoagulation, early treatment was started using LMWH at only 15 h after surgery, although clinical signs of bleeding were absent. We believe that the success of this approach is related to specific dose assessments using the anti-FXa assay, as it is suited for monitoring patients who are receiving LMWH and provides the most accurate assessment of the anticoagulation effect. The anti-FXa assay should be ordered as a "peak" test at 3–4 h after the LMWH treatment, when the blood levels are expected to be highest. Our initial treatment targeted the prophylactic ranges (0.32), although the dose was subsequently increased to 0.6 because the lower dose was not effective. The patient subsequently experienced complete regression of venous thrombosis, had no ischemic foci on the brain CT scan, and was discharged with clear consciousness and no clinical or laboratory signs of hypercoagulation.

Conclusion

Hypercoagulability is common during the acute period of aSAH, and leads to microthrombosis and ischemic foci, although standard coagulation testing may not detect these changes. Thus, thromboelastometry may be effective for evaluating hemostasis using whole blood, as it is sensitive to even minor shifts in hemostasis. Furthermore, adequate prophylaxis and hypercoagulation therapy after aSAH may help to prevent DCI and improve neurological outcomes, although further studies are needed to evaluate this approach.

Conflict of Interest The authors declare no conflicts of interest.

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