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The Effect of Treatment with tPA on Factor VIII Elevation

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Abstract

Factor VIII (FVIII), an integral part of the clotting process, has been associated with increased incidence of acute ischemic stroke (AIS) when elevated. Intravenous tissue plasminogen activator (IV tPA) is a clot-busting drug and is the only FDA approved treatment for AIS. The effect of IV tPA on FVIII levels has not yet been explored in the context of ischemic stroke.

This case report will examine three unique cases and the effect of IV tPA administration on severely elevated FVIII levels. In case 1, the FVIII level decreases steadily to normal levels, post-tPA administration. In case 2, the FVIII level decreases dramatically in the acute phase post-tPA and then rises steadily to near-baseline level. Finally, in case 3, the FVIII level increases post-tPA and then remains consistently elevated for the duration of the acute phase.

The purpose of this case report is to explore the potential relationship between IV tPA and FVIII levels with respect to recanalization and post-stroke level of functioning.

Keywords: Factor VIII; Blood coagulation; Thrombosis; Thrombolytic; Ischemic stroke

Abbreviations

IV TPA: Intravenous Tissue Plasminogen Activator; AIS: Acute Ischemic Stroke; FVIII: Factor VIII; mRS: Modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale; CTA: CT angiography; MRI: Magnetic Resonance Imaging; MRA: Magnetic Resonance Angiography; INR: International Normalized Ratio

Background

Intravenous recombinant tissue-type plasminogen activator (IV tPA), a thrombolytic agent, is the only medication approved by the Food and Drug Administration for treatment of acute ischemic stroke (AIS). Currently, IV tPA is recognized as the most effective treatment, and therefore the standard of care, in the acute setting of ischemic stroke [1-4].

A growing body of research has demonstrated the association between elevated levels (>150% activity) of coagulation factor VIII (FVIIII) and incident ischemic stroke [5]. Recent studies have also suggested that elevated FVIII may be associated to adverse in-hospital events and outcomes in the setting of AIS [6,7]. Furthermore, some evidence exists that FVIII levels may be impacted following the administration of IV tPA.

The following cases will explore three scenarios in which tPA was administered to AIS patients whose FVIII levels were elevated as classified by the laboratory-defined reference range of 50-150% activity.

Case Presentation

Case 1: Elevated FVIII pre-tPA reduced to normal post-tPA

Case 1 is a 48 year old Caucasian male with no significant past

Table 1: Admission Information.

	Case 1	Case 2	Case 3
Systolic Blood Pressure	122	225	144
Diastolic Blood Pressure	58	100	127
HbA1c	5.2	5.7	5.6
White Blood Cell Count	5.8	8.7	5.1
Platelets	207	181	178
Hematocrit	42.4	46.7	46.8
PT	11.7	11.2	11.5
INR	1.1	1.0	1.1
PTT	22.3	20.9	24.4
Triglycerides	78	74	125
HDL	50	42	50
LDL	126	143	111
NIH Stroke Scale			
1a. Level of Consciousness	0	2	0
1b. Questions	0	2	0
1c. Commands	0	2	0
2. Best Gaze	2	2	0
3. Visual Fields	2	0	1
4. Facial Paresis	2	1	1
5. Right Upper Motor	0	4	0
6. Left Upper Motor	4	0	1
7. Right Lower Motor	0	3	0
8. Left Lower Motor	3	0	1
9. Limb Ataxia	0	0	0
10. Sensory	2	2	0
11. Language/Aphasia	0	3	1
12. Dysarthria	1	2	1
13. Neglect	2	2	1
Total NIHSS Score	18	25	7

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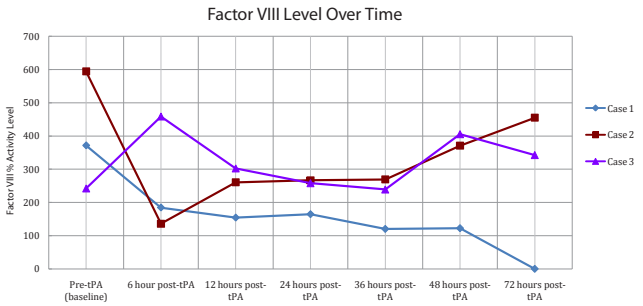

Figure 1: Factor VIII Level over Time.

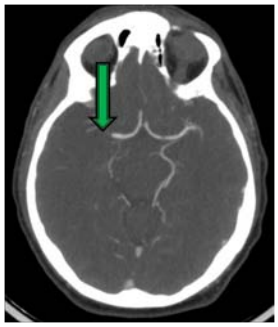

Figure 2: This image set references Case 1: Shows the CT angiogram abrupt cutoff of the right middle cerebral artery (arrow). Before IV tPA, the proximal right middle cerebral artery was occluded. This segment had recanalized with IV tPA, leaving a large branch occluded.

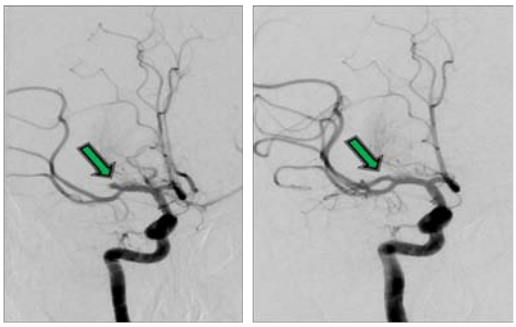

Figure 3: This image set references Case 1: pre- and post-endovascular therapy angiogram images revealing recanalization of the right middle cerebral artery branch.

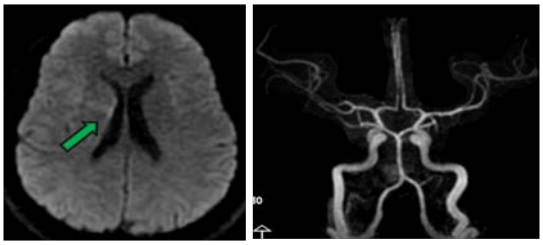

Figure 4: This image set references Case 1: (Right) shows a tiny area of completed infarct in the periventricular region on the right side. (Left) The fourth image reveals sustained complete recanalization of the right middle cerebral artery and its branches.

medical history and no reported tobacco, alcohol, or illicit drug use. Prior level of function was completely independent as measured by the modified Rankin Scale score (mRS = 0). The mRS ranges is the most commonly used functional outcome measure for stroke, ranging from 0 (no symptoms) to 6 (deceased). Upon admission, the patient exhibited normal baseline blood pressure and laboratory values with the exception of FVIII level which was severely elevated at 371.1% (Table 1, Figure 1).

At baseline, the patient had a right middle cerebral syndrome with NIH Stroke Scale (NIHSS) score of 18 (Table 1). The NIHSS examination is the most commonly used tool to quantify the degree of impairment and evaluate response to treatment of stroke. Scores less than 5 are considered minor, 5-15 moderate, 16-20 moderate to severe, and >20 severe strokes [8]. CT angiography (CTA) confirmed the presence of a proximal right middle cerebral artery occlusion (Figure 2).

The standard bolus dose of tPA based on the patient's weight (59 mg) was administered 28 minutes after hospital arrival and 65 minutes after symptom onset. The patient had minimal improvement in motor function during the tPA infusion, so he was treated with adjuvant intra-arterial therapy. The clot was removed with a stentriever device. Complete recanalization was achieved 162 minutes after onset of symptoms (Figure 3). Magnetic resonance imaging (MRI) revealed a tiny focus of completed infarction and magnetic resonance angiography (MRA) revealed sustained recanalization (Figure 4).

Within 6 hours of tPA administration, the patient's FVIII level had decreased by more than 50% to 184.4%. The patient's FVIII levels continued to decline over the course of his admission and at 48 hours post-tPA had decreased to 122.2%, a 67% reduction from the baseline level (Table 2, Figure 1).

The patient's stroke etiology was possibly cardioembolic, due to the presence of a patent foramen ovale, but no clot was found in his lower extremities on ultrasound. His NIHSS score on discharge was 0 with an mRS score of 1. The patient had no inpatient complications and was discharged to home. At 90 days, his NIHSS remained 0, his mRS score was 0, and his FVIII level was 100.1%.

Case 2: Elevated FVIII pre-tPA reduced to normal and returned to elevated post-tPA

Case 2 is a 73 year old Black male with a history of hypertension, no other significant medical history, no reported tobacco or illicit drug use, and occasional alcohol use. Prior level of function was independent (mRS = 0). Upon admission, the patient exhibited elevated blood pressure, but otherwise unremarkable laboratory findings with the exception of FVIII level which was severely elevated at 593.9% (Table 1, Figure 1).

At baseline, the patient's NIHSS score was 25 and consistent with a left hemispheric syndrome (Table 1). CTA revealed occlusion of the

Table 2: Factor VIII Levels during Acute Hospitalization.

	Case 1	Case 2	Case 3
Pre-tPA (baseline)	371.1	593.9	242.3
6 hours post-tPA	184.4	136.1	458.4
12 hours post-tPA	154.1	260.5	302.4
24 hours post-tPA	164.3	266.5	258
36 hours post-tPA	120	269.1	239.1
48 hours post-tPA	122.2	370.8	405.2
72 hours post-tPA	*	453.9	342.5

*Patient was discharged prior to 72 hours

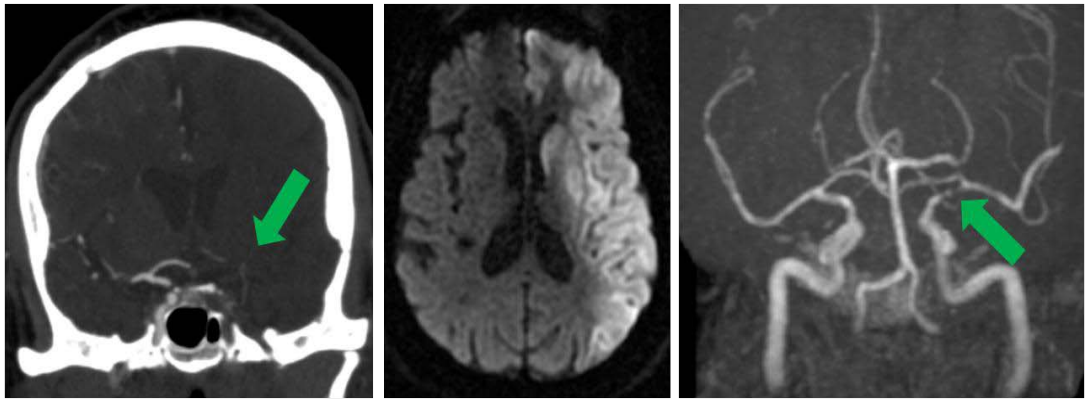

Figure 5: This image set references Case 2: (Left) reveals an occluded terminal carotid artery with no filling of the left middle cerebral artery. (Middle) Reveals completed infarct in the left anterior and middle cerebral artery territories. (Right) Demonstrates that recanalization had occurred, but with an underlying stenosis of the left internal carotid artery.

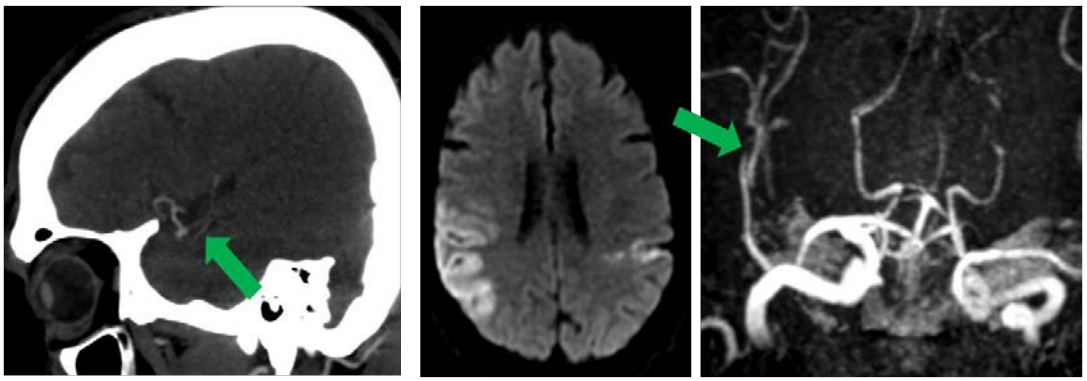

Figure 6: This image set references Case 3: (Left) Sagittal image of the right hemisphere demonstrating an occlusion of a branch of the middle cerebral artery (arrow). (Middle) Axial cut revealing completed infarction in both hemispheres. (Right) demonstrates persistent occlusion of a branch of the right middle cerebral artery.

left terminal internal carotid artery with extension of clot into the left anterior and middle cerebral arteries (Figure 5).

The standard bolus dose of tPA based on the patient's weight (79.5 mg) was administered 62 minutes after hospital arrival and 100 minutes after symptom onset. Post-tPA, the patient's MRA revealed complete recanalization with residual moderate stenosis of the left terminal internal carotid artery (Figure 5). Unfortunately, his infarct was completed and involved nearly the entire left hemisphere.

Within 6 hours of tPA administration, the patient's FVIII level decreased by more than 75% to 136.1%, which is classified as a normal FVIII level. However, by 12 hours post-tPA, the patient's FVIII level had increased to 260.5% and continued to rise steadily during hospitalization. By 72 hours post-tPA, the patient's FVIII level had returned to 454.9%, a severely elevated level. The patient's FVIII measurements are shown in Table 2 and Figure 1.

The patient's stroke etiology was large artery disease. His NIHSS score on discharge was 20 with an mRS score of 5. The patient had no inpatient complications and was discharged to inpatient rehab. At 90 days, his NIHSS was 18, his mRS was 5 (bedridden/complete dependence), and his FVIII level was 596.8%.

Case 3: Elevated FVIII pre-tPA minimally changed post-tPA

Case 3 is a 65 year old Black male with a history of hypertension, congestive heart failure and possible atrial fibrillation for which he was taking Coumadin prior to the stroke event. The patient is a current smoker with reported alcohol and occasional illicit substance use. Upon admission, his blood alcohol level was <3 mg/dL, but the patient tested positive for cocaine. Prior level of function was independent (mRS=0). Upon admission, the patient exhibited elevated blood pressure, but otherwise unremarkable laboratory findings with the exception of FVIII level which was severely elevated at 242.3% (Table 1, Figure 1).

At baseline, the patient's NIHSS score was 7consistent with a right middle cerebral artery syndrome (Table 1). CTA demonstrated occlusion of the inferior division of the right middle cerebral artery (Figure 6). The patient was treated with standard dose intravenous tPA 55 minutes after arrival and 93 minutes after onset. MRI demonstrated complete infarction in the involved right middle cerebral artery territory and a few unanticipated small foci of infarction in the left hemisphere. MRA revealed persistent occlusion of the right middle cerebral artery branch.

Within 6 hours of tPA administration, the patient's FVIII level increased by more than 89% to 458.4. By 12 hours post-tPA, the patient's FVIII level had decreased to 302.4 and continued to decrease until 48 hours post-tPA at which time it dramatically increased to 405.2. By 72 hours post-tPA, the patient's FVIII level had exceeded the baseline level by 41% to a level of 342.5 (Table 2, Figure 1).

The patient's stroke etiology was atrial fibrillation with subtherapeutic international normalized ratio (INR). His NIHSS on discharge was 0, but his mRS was 3 (required assistance for some activities, but was able to walk without support of another person) and he was discharged to inpatient rehab. He was lost to follow-up.

Discussion

These cases demonstrate a potential link between recanalization due to tPA administration and FVIII level. All three patients described presented with a severely elevated FVIII level at baseline and all patients were given tPA within the FDA-recommended 3-hour treatment window. These patients were participants, after informed consent, in a clinical trial approved by our Institutional Review Board.

Case 1's FVIII level decreased continually over the acute period, complete recanalization was achieved, and the patient was discharged to home with no deficits and almost no disability. Normal FVIII persisted at 90 days post stroke. The elevated FVIII level in Case 1 may have been the cause or the consequence of the acute thrombus. The decline may have represented an epiphenomenon of recanalization. Since the patient's FVIII level remote from the stroke was normal, this argues against his peri-stroke FVIII representing a constitutional risk factor for thrombosis.

Case 2's FVIII level decreased dramatically within 6 hours post-tPA, concurrent with recanalization, but gradually increased as his baseline level. For that patient, recanalization was achieved, but severe infarction occurred prior to recanalization and the patient moved to inpatient rehab with severe disability. His disability and severely elevated FVIII level persisted at 90 days. Similar to Case 1, the elevated FVIII level could have been the cause or the consequence of the acute thrombus. His level declined abruptly with recanalization, but then increased during his admission and remained elevated at follow-up. The decline in FVIII level is thought to represent a surrogate marker of recanalization. Since his FVIII level was severely elevated remote from the stroke, this may indicate a constitutional risk factor for thrombosis.

Finally, Case 3's FVIII level was severely elevated before tPA and increased after tPA, remaining severely elevated. In contrast to Cases 1 and 2, no recanalization occurred in response to tPA. The persistent elevation in FVIII after tPA may be a surrogate marker for lack of recanalization. Unfortunately, we were not able to secure a FVIII level remote from the patient's stroke; therefore, it is impossible to determine if this patient's elevated FVIII represented an epiphenomenon of acute stroke or a constitutional risk factor.

These three cases suggest that recanalization after tPA administration may be related to the degree of change in FVIII level that occurs during the acute phase of stroke. Further study is necessary to determine what the dynamic changes in FVIII levels mean in the acute setting of stroke and whether there is clinical utility to measuring serial levels in the population of ischemic stroke patients who receive recanalization therapies.

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