



## Case Report

# Delayed recurrence of acute subdural hematoma in a patient with plasminogen activator inhibitor mutation

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## ABSTRACT

**Background:** Plasminogen activator inhibitor type I (PAI-1) is important for balancing the fibrinolytic effect of plasmin, and deficiency can result in increased risk of bleeding. We report a case of a patient with PAI-1 deficiency who presented with delayed spontaneous recurrence of an acute subdural hematoma (aSDH) after evacuation.

**Case Description:** A 29-year-old male presented with altered mental status (AMS) after a fall at a construction site with Glasgow Coma Scale (GCS 4T). His coagulation profile was normal, and brain computed tomography (CT) showed a left-sided aSDH. He underwent emergent evacuation of the hematoma. On postoperative day 2, he was started on heparin for venous thromboembolism (VTE) prophylaxis. His neurological examination improved and was discharged with no focal deficits. Three days later, he presented with sudden AMS (GCS 7T); CT head showed a large hematoma at the site of original surgery. The hematoma was evacuated emergently. On readmission, the family informed providers that the patient had a history of PAI-1 deficiency. Postoperatively, only mechanical VTE prophylaxis was used and the patient was started on oral TXA per hematology recommendation. The patient improved and was discharged with no focal deficit. On follow-up, he remained neurologically stable.

**Conclusion:** PAI-1 deficiency should be suspected in patients with delayed posttraumatic/surgical bleeding and a normal coagulation profile. If PAI-1 deficiency is evident or suspected, then a trial of antifibrinolytic agent should be used to treat and prevent recurrence of bleeding. Furthermore, chemical VTE prophylaxis should be avoided as it increases the risk for bleeding.

**Keywords:** Fibrinolysis, Plasminogen activator inhibitor, Subdural, Tranexamic acid, Trauma

## INTRODUCTION

Plasminogen and its activation system are an important part of the normal coagulation cascade as they promote fibrinolysis of mature thrombi.<sup>[3]</sup> Their effect is balanced by the plasminogen activator inhibitor type I (PAI-1).<sup>[4]</sup> Elevated levels of PAI-1 are associated with increased risk of arterial thrombosis, while low levels are associated with increased risk of bleeding.<sup>[7]</sup> To date, there are two genetic mutations associated with PAI-1 deficiency which have been documented.<sup>[1]</sup> We report a rare case of an Amish patient with a known heterozygous PAI-1 mutation that presented with delayed spontaneous recurrence of an acute subdural hematoma (aSDH) after a successful initial surgical evacuation.

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## CASE DESCRIPTION

The patient is a 29-year-old Amish male who presented with altered mental status (AMS) after a fall from height. His initial Glasgow Coma Scale (GCS) was 4T with a dilated nonreactive left pupil. His computed tomography (CT) of the brain showed an acute left-sided aSDH with a 15 mm rightward shift [Figure 1]. His coagulation profile and complete blood count were within normal limits, and because of the patient's poor GCS and amount of shift, we performed an emergent left-sided decompressive craniectomy with evacuation of the aSDH. On postoperative day (POD) 1, he did improve neurologically to a GCS of 11T. On POD 2, he was started on subcutaneous heparin for venous thromboembolism (VTE) prophylaxis. On POD 13, he was discharged to a rehabilitation facility with GCS15 and no focal deficit.

The patient presented 3 days later with sudden AMS that was preceded by a sudden headache. His GCS was 7T and CT head showed large aSDH at the site of previous surgery [Figure 2]. He was taken for an emergent evacuation of the hematoma. The family revealed that multiple family members had PAI-1 deficiency including the patient himself. Postoperatively, we only used mechanical VTE prophylaxis. After consultation with the hematology team, the patient was started on oral TXA (1300 mg) 3 times a day for 21 days based on the hematology team recommendations. His neurological status gradually improved and was discharged to a rehabilitation facility on POD 5 with GCS 15 and no focal deficit. Notably, performing an initial craniectomy instead of craniotomy might have added a protective effect during the second bleeding episode. On 3 weeks outpatient follow-up, the patient remained neurologically stable.

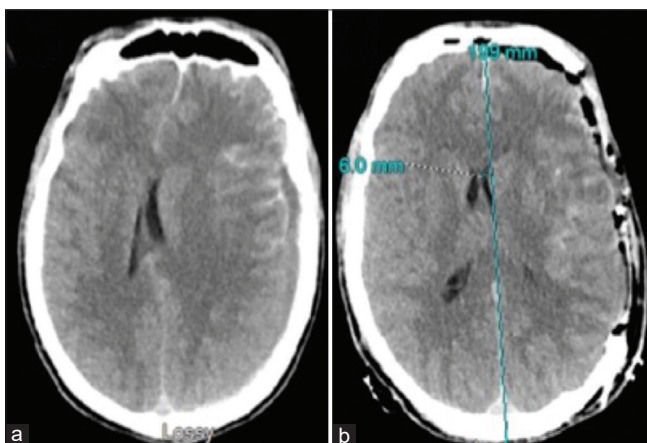
## DISCUSSION

Plasmin is the primary enzyme responsible for fibrinolysis and is formed by the action of tissue plasminogen activator

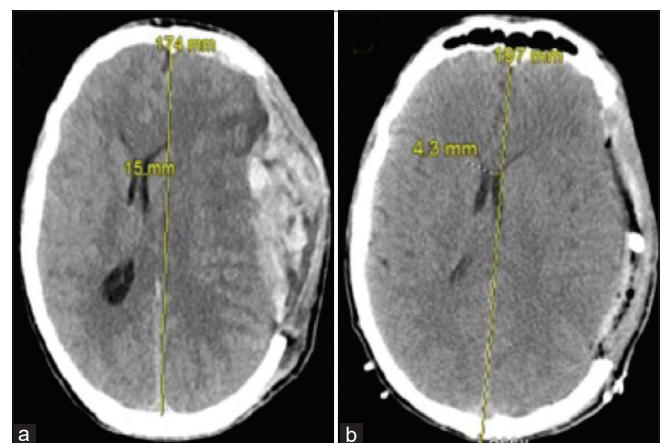
on plasminogen.<sup>[3]</sup> PAI-1 plays a key role in the controlled degradation of thrombi within the circulation as it binds to plasminogen activators and results irreversible inhibition. PAI-1 dysfunction usually suspected in patients with a history of delayed postsurgical bleeding and normal standard coagulation tests (e.g., prothrombin time, activated partial thromboplastin time, and thrombin clotting time).<sup>[5,8]</sup> Furthermore, the presence of hyperfibrinolysis is another factor that points toward PAI-1 related bleeding.<sup>[5,8]</sup> The confirmation of PAI-1 deficiency requires specific assays, such as the PAI-1 antigen level (positive test if the antigen is undetectable) and activity (positive test if activity <1 IU/mL).<sup>[1,2]</sup>

The management of patients with PAI-1 deficiency requires a multistep approach, and it is important to coordinate with the hematology team as they have the required expertise to guide the process [Figure 3]. For bleeding prevention, antifibrinolytics (e.g., TXA) should be used before and after any surgical procedure. The dosage and duration are guided by the type of the intervention, body weight, and the route of administration. Furthermore, medications that affect coagulation such as aspirin, heparin, warfarin, and others should be avoided.<sup>[5]</sup> Therefore, only mechanical thromboprophylaxis should be considered in these patients. In this case, and during the first episode, the patient did not receive TXA and was started on chemical VTE prophylaxis because the treating team was unaware of the patient history of PAI-1 deficiency, which potentially increased the patient's rebleeding risk.

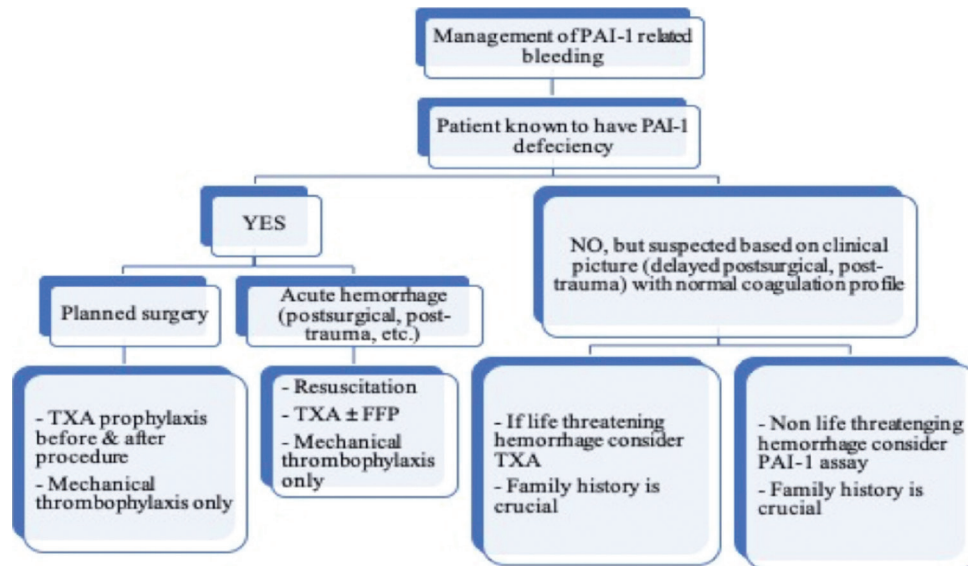
For the treatment of acute hemorrhage (e.g., intracranial hemorrhage with or without evacuation), the administration of intravenous antifibrinolytics (e.g., TXA) is effective in controlling the bleeding in PAI-1 patients.<sup>[5]</sup> The CRASH-3 trial has demonstrated that the use of TXA in trauma patients is safe as it did not result in increased



**Figure 1:** A computed tomography scan of the brain that shows the patient's initial acute subdural hematoma before surgery (a) and after evacuation (b).



**Figure 2:** A computed tomography scan of the brain that shows the patient's recurrent acute subdural hematoma (a) and after the second evacuation (b).



**Figure 3:** A decision tree that summarizes the steps to consider when managing patients with plasminogen activator inhibitor type I in different clinical scenarios.

risk of vascular occlusion.<sup>[9]</sup> In this case, the patient was started on oral TXA for 21 days to prevent recurrence after the second surgery. Fresh frozen plasma (FFP) can also be used as a temporary measure to increase PAI-1 activity before achieving the therapeutic steady-state level of antifibrinolytics. Notably, FFP alone is not a viable option to replace PAI-1 because of the need for repeated infusion, which may increase the risk of volume overload and/or infusion reactions.<sup>[6]</sup>

The patient education regarding bleeding manifestations and when to seek treatment is important. Furthermore, patients should be offered genetic counseling, since PAI-1 deficiency is inherited in an autosomal recessive manner.<sup>[5]</sup>

## CONCLUSION

PAI-1 deficiency is a rare hereditary bleeding disorder that was recently discovered. It should be considered in patients with delayed posttraumatic or postsurgical bleeding, especially in a population known to harbor the genetic mutation (e.g., Amish). If PAI-1 deficiency is established or highly suspected, then a trial of antifibrinolytic agents (e.g., TXA) should be considered. They can also be used as prophylaxis to prevent bleeding in patients with PAI-1 deficiency before any surgical intervention. Finally, chemical VTE prophylaxis puts the patients at risk of bleeding.

## Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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