Intraparenchymal Hemorrhage in a Patient With Osteogenesis Imperfecta and Plasminogen Activator Inhibitor-1 Deficiency

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Background: Osteogenesis imperfecta is associated with susceptibility to connective tissue damage, including intracranial but usually extra-axial hemorrhage. Plasminogen activator inhibitor-1 deficiency is a rare fibrinolytic cause of systemic bleeding diathesis.

Objective: To describe a case of a brainstem intraparenchymal hemorrhage associated with connective tissue and coagulation disorders.

Design: Case report.

Setting: Academic medical center.

Patient: A 36-year-old woman with a history of osteogenesis imperfecta presented to the emergency department after an argument, during which she developed left ear pain and right eye esotropia followed by quadriparesis and somnolence. Neuroimaging showed a tegmental mesencephalic hemorrhage.

Main Outcome Measures: Results of computerized tomography, magnetic resonance angiography, and parenchymal imaging; and serum hematologic markers.

Results: No underlying vascular abnormality or mass lesion was found. Among coagulopathic serum markers, only plasminogen activator inhibitor-1 activity level was abnormally low.

Conclusion: Intraparenchymal hemorrhage may occur in the setting of a fibrinolytic inhibitory deficiency and osteogenesis imperfecta.

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O F THE 10% TO 15% OF strokes that are caused by nontraumatic intraparenchymal (ie, intracranial and intra-axial) hemorrhage, most are spontaneous, presumed to be due to hypertension or amyloid angiopathy, and are classified as primary. In fewer than 25% of cases is an underlying abnormality, such as vascular malformation, tumor, or coagulopathy, found. This is a case report of an unusual spontaneous intraparenchymal hemorrhage in a patient with osteogenesis imperfecta and plasminogen activator inhibitor-1 activity deficiency.

REPORT OF A CASE

A 36-year-old woman with a history of osteogenesis imperfecta presented after an argument with her son. She first noted a sudden pain in her left ear associated with a feeling of being light-headed. Then she felt her right eye turning in, found it difficult to speak, and felt that she would pass out. She lost consciousness in the ambulance that took her to the hospital.

When she was first examined in the emergency department, she was comatose and did not awaken to stimuli. Her right eye was deviated down and in, and her eyes remained skewed downward. There was limited upgaze. On left gaze there was torsional nystagmus. The right pupil was 4 mm, the left 4.5 mm; each reacted to light. She moved the left limbs better than the right to noxious stimuli. Noncontrast head computed tomography showed and brain magnetic resonance imaging (Figure) confirmed a left tegmental mesencephalic hemorrhage. Toxicology screen results were negative.

On the second hospital day, the patient became more alert. After extubation, she noted vertical diplopia and hypesthesia on the left side of her face and right arm. Her sclerae were blue. Her right eye was deviated down and in; her left eye was also deviated inward. On upgaze, there were convergence movements of both eyes.

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Computed tomographic angiography and follow-up magnetic resonance angiography, including time-of-flight sequencing, showed no underlying tumor or vascular malformation. No additional areas of hemorrhage were found. Serum coagulation cascade markers, platelet function studies, the von Willebrand factor, and fibrinolytic markers α2-antiplasmin and plasminogen activator inhibitor-1 (PAI-1) antigen levels were normal. However, PAI-1 activity was undetectable.

**COMMENT**

Osteogenesis imperfecta is a connective tissue disorder with varying clinical presentations, typified by bone fragility, ligamentous laxity, and easy bruising. Rarely, osteogenesis imperfecta is complicated by intracranial bleeding. Case reports, most often in pediatric populations, have described epidural, subdural, subarachnoid, and retinal hemorrhages.

Four subtypes, based on particular collagen mutation and phenotype, are described. Classic, type 1 osteogenesis imperfecta is characterized by bluish sclerae and, typically, COL1A1 or COL1A2 gene mutation. Collagen mutations in osteogenesis imperfecta lead to platelet dysfunction and vascular wall fragility, which account for easy bruising and hemorrhages due to trivial trauma. The relative scarcity of type 1 collagen in smaller intracerebral vessels may account for the predominance of subdural or subarachnoid over intraparenchymal hemorrhages in osteogenesis imperfecta. Nontraumatic spontaneous intraparenchymal hemorrhage in osteogenesis imperfecta has not, to our knowledge, been previously described.

In our patient, the additional finding of PAI-1 activity deficiency likely contributed to her hemorrhage. Plasminogen activator inhibitor-1 is a main inhibitor of tissue-type and urokinase-type plasminogen activators. Elevated plasma PAI-1 levels have been associated with myocardial infarction and venous thrombosis. Deficiencies in PAI-1 have been found in patients with a predilection for easy bruising or bleeding from trivial trauma. Plasminogen activator inhibitor-1 deficiency has been characterized either by reduced expression of the protease inhibitor or by decreased activity of normal amounts of PAI-1 (eg, PAI-1 activity deficiency). Structural abnormalities affecting the PAI-1 molecule’s binding capacity to plasminogen activator or the presence of PAI-1–binding antibodies have been suggested as reasons for decreased functional activity despite normal measured levels of PAI-1.

The tegmental mesencephalic hemorrhage was in an unusual location. The patient had no history of hypertension nor was she hypertensive during her hospital admission or afterwards. Vascular imaging excluded a vascular malformation. There had been no trauma. We posit that our patient’s collagen disease and fibrinolytic inhibition deficiency, in the setting of situational hypertension, caused the intraparenchymal hemorrhage.

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REFERENCES


New Initiatives: Clinical Trials and Videos. We have embarked on 2 new initiatives: Clinical Trials and video presentations. We welcome manuscripts that describe double-blind, randomized, placebo-controlled clinical trials as our primary area of interest. We plan on expediting the review process and time to publication and to include them online ahead of print as these studies are time sensitive and of direct benefit to our patients. We hope you will take advantage of this new initiative. Please refer to the Instructions for Authors when submitting a Clinical Trials paper, including the requirement to register the trial with an accepted clinical trials site.

We plan to utilize videos as part of published papers that highlight and provide convincing information about the observational and visual features of a patient’s neurologic findings. Please refer to Instructions for Authors for instructions on submitting video presentations.