Mystery Case: Clinical Reasoning

Recurrent cerebral ischemia during pregnancies

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Section 1

A 29-year-old G6P3023, left-handed woman presented with acute onset left-sided weakness and expressive aphasia. She was in her normal state of health while driving home from work when her mother noted symptom onset. She was taken immediately to the emergency department for further evaluation. On presentation, she was afebrile with blood pressure 136/99 mm Hg, regular heart and respiratory rates, and oxygen saturation 88% on room air. Neurologic examination was notable for left-sided hemiparesis and sensory disturbance. The aphasia had resolved. Emergent head CT did not demonstrate any abnormalities.

The patient reported that 4 years ago, during her previous term pregnancy, she developed transient neurologic symptoms characterized by right-sided weakness lasting less than 24 hours. She was not offered tissue plasminogen activator (tPA) during that encounter, as she presented outside the time window, and exhibited no residual deficits thereafter. She was sexually active and denied use of contraception. She denied headache, loss of consciousness or trauma, changes in vision, chest pain, or shortness of breath at this time.

The patient did not have any contraindications to and was thus offered recombinant tPA. However, she and her family refused administration of tPA due to a family history of intracranial hemorrhage status post tPA administration in her maternal aunt. To help guide further diagnostic decision-making, she underwent a pregnancy test. Her pregnancy test result was positive (β -hCG 39.5 units/mL).

Questions for consideration:

1. Is pregnancy alone a contraindication for IV tPA administration?
2. What diagnostic considerations should be considered in pregnant patients?
3. What additional laboratory evaluation is indicated in pregnant patients with recurrent cerebrovascular events?
4. What additional risk factors may predispose the patient to recurrent cerebral ischemia during pregnancy?

GO TO SECTION 2

Section 2

Recombinant tPA is categorized as pregnancy class 3 and does not cross the placenta.¹ Current guidelines recommend that tPA should not be categorically withheld in pregnancy-associated ischemic stroke, but a risk–benefit analysis, including the risks of uterine bleeding, should be discussed with each patient.^{1,2}

Ischemic stroke during pregnancy is rare and is typically associated with the same risk factors as stroke in the general population. However, pregnancy is associated with an increased risk of stroke, highest in the peripartum and postpartum periods due to a progressing hypercoagulable state. Concentrations of factors VIII, IX, and X and von Willebrand factor increase, while concentrations of antithrombin III and protein S decrease, augmented by protein C resistance.¹ Physiologic changes in blood volume, cardiac output, autonomic tone, and hormones during pregnancy may interfere with atrial electrical mechanics, predisposing to atrial fibrillation. Other predisposing factors include structural heart disease and the use of tocolytics during delivery.³ Laboratory testing may include a hypercoagulability panel as well as studies of infectious and noninfectious inflammatory etiologies.¹

Diagnostic and treatment decisions can be challenging because of exposure to the fetus. Noncontrast MRI and ultrasonography are considered safe during pregnancy and the

imaging techniques of choice. The use of gadolinium contrast for MRI should be limited as it can cross the placenta and may have teratogenic effects.⁴ CT may be used in the diagnostic evaluation as expected radiation exposure is often less than the exposure known to cause fetal harm. However, iodinated contrast agents for CT can cross the placenta, and despite a lack of studies demonstrating teratogenic effects, should be employed only if determined to be categorically critical for treatment purposes.⁴

Our patient underwent emergent brain MRI, which demonstrated bihemispheric punctate lesions of restricted diffusion (figure). Brain magnetic resonance angiography (MRA) and carotid ultrasound revealed no abnormalities, including no large vessel occlusion or hemodynamically significant stenoses. Her deficits resolved during the first 24 hours of hospitalization.

A more detailed family history was obtained following emergent evaluation. Our patient reported a family history of bleeding, including her mother's recurrent epistaxis and her maternal aunt's postthrombolysis fatal intracranial hemorrhage. She reported a history of spontaneous epistaxis, occurring 3–4 times per year, never requiring hospitalizations nor transfusions. She denied any additional sites of bleeding. She had never been formally tested for hereditary coagulation disorders and none of her children had demonstrated spontaneous bleeding.

Figure Brain and lung imaging

(A, B) MRI brain with evidence of bihemispheric ischemic stroke (yellow arrows demonstrate areas of restricted diffusion). (C) CT chest coronal view with evidence of a pulmonary arteriovenous malformation (AVM) (red arrow). (D, E) Digital subtraction angiography of the chest demonstrates a pulmonary AVM (D; red arrow) and the embolization of the AVM (E; red arrow).

Cardiac evaluation, including a 12-lead ECG, continuous cardiac telemetry, and transthoracic and transesophageal echocardiogram, was unrevealing for sources of embolism; however, no contrast agent was used, consistent with our institution's policy for pregnant patients. Lower extremity Doppler studies were negative. Blood counts, electrolytes, liver and renal function, lipid profile, and hemoglobin A1C were within normal limits. Additional serum laboratories were negative including hypercoagulability panel, inflammatory markers, rheumatologic panel, and infectious panel following the recommendations of Singhal et al.⁵

Thus this young woman presented with cerebral ischemic attacks during sequential pregnancies, with a history significant for epistaxis and a familial bleeding disorder, with borderline hypoxia and unremarkable laboratory, cardiac, and cerebrovascular evaluations.

Questions for consideration:

1. What diagnosis would you suspect based on the clinical history?
2. What additional screening tests should be considered?

GO TO SECTION 3

Section 3

After meeting with the patient and her family to discuss the risks and benefits of further evaluation and possible treatment indications, she underwent chest CT angiography (CTA), liver MRI, and complete spine MRI to evaluate for arteriovenous malformations (AVMs) as a source of paradoxical embolism. Liver and spine MRIs were unremarkable. Chest CTA demonstrated multiple bilateral pulmonary AVMs. She underwent urgent and successful embolization of 7 pulmonary AVMs (figure).

Given the history of epistaxis, pulmonary AVMs, and family history of bleeding, we counseled the patient on the suspected diagnosis of hereditary hemorrhagic telangiectasia (HHT). Genetic testing revealed she had a 1429-1G>A sequence change in the *ENG* gene consistent with a diagnosis of HHT type 1.

Discussion

HHT is also known by the eponyms Osler-Weber-Rendu syndrome for their descriptions in the late 19th and early 20th centuries.⁷ HHT is now known to be an autosomal dominant disease with a prevalence of at least 1/5,000 persons, although estimates vary by region.^{6,7}

Early diagnosis of HHT relies upon clinical features including a history of epistaxis (spontaneous and recurrent) as well as telangiectasias of the lips, buccal mucosa, face, and hands. Epistaxis is the most common manifestation of HHT, typically presenting in the early teenage years, affecting nearly all individuals by age 40.⁶ Roughly two-thirds of telangiectases occur before age 40.⁶ Diagnosis of HHT should be considered in a patient presenting with this constellation of symptoms, enhanced by a known family history of bleeding or a diagnosis of an AVM. In 2000, Shovlin et al.⁷ published the Curaçao Criteria for the diagnosis of HHT, which includes epistaxis, telangiectases and visceral lesions (at characteristic sites: gastrointestinal, pulmonary, hepatic, spinal, and cerebral), and a family history of HHT. The diagnosis of HHT is considered definite when 3 or more criteria are met, suspected when 2 criteria are present, and unlikely if fewer than 2 criteria are present. Genetic testing can be used to establish the diagnosis in inconclusive clinical presentations.⁷

Genetic testing can begin with sequence analysis for a heterozygous pathogenic variant of *ENG* (HHT type 1) or *ACVRL1* (HHT type 2) or a multigene panel including the rarer mutant genes *SMAD4* and *GDF2*.⁶ *ENG* and *ACVRL1* encode endoglin and activin A receptor type II-like 1, respectively, 2 proteins involved in the transforming growth factor β family, which mediate vascular remodeling.⁶ Mutations in *ENG* are associated with a higher prevalence of pulmonary AVMs, whereas mutations in *ACVRL1* have a

higher prevalence of hepatic AVMs and a more benign clinical course.⁶ Genetic counseling remains a significant aspect in the care of families with HHT including family planning as well as screening at-risk family members.

Screening is directed at visceral AVMs, which can lead to substantial morbidity and mortality if undiagnosed. The evaluation and management of pulmonary AVMs, gastrointestinal telangiectasias, and liver AVMs should be individualized. Detection of cerebral AVMs may be achieved with a combination of MRI and MRA, but CTA is more sensitive to detect associated aneurysms and digital subtraction angiography remains the gold standard.⁸ Investigational therapies aimed at disrupting the development and progression of these abnormal vascular connections lack controlled trials.

CNS manifestations of HHT include cerebral abscesses, intracranial hemorrhage, and ischemic stroke. Ischemic stroke is usually the result of paradoxical thromboemboli passing through pulmonary AVMs, but may also be caused by hyperviscosity due to chronic hypoxemia.⁹

Most women with HHT proceed with normal pregnancies, although those with pulmonary AVMs should be aware of life-threatening complications such as AVM hemorrhage, ischemic stroke, and maternal death.¹⁰ Most complications are the result of the complex hemodynamic changes associated with increased maternal blood volume and cardiac output and decreased systemic vascular resistance occurring in the second and third trimesters. Women with HHT should be screened prior to pregnancy for pulmonary AVMs and treated accordingly.¹⁰

Upon discharge, our patient was referred to our high-risk pregnancy care and family birth center, where she received care through the delivery of her baby girl. She continues to be followed at our University's HHT Center of Excellence.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

Name	Location	Contribution
Zachary Bulwa, MD	University of Chicago	Manuscript drafting/revision, literature review, data analysis and interpretation, formatting of figures, patient care

Appendix (continued)

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Laura P. Dresser, MD	University of Chicago	Manuscript drafting/revision, literature review, data analysis and interpretation, patient care
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Scott Mendelson, MD, PhD	University of Chicago	Manuscript revision

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Mystery Case responses

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group email sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media.

A total of 278 individuals submitted complete responses to the Mystery Case. Of these, 9 respondents answered all questions correctly. The majority of respondents (85.1%)

were correct that pregnancy is not a contraindication for tPA. However, only 23.2% recognized that tPA is a class 3 drug that does not cross the placenta.

Most of the respondents (68.2%) correctly diagnosed the patient with HHT. In one study, stroke was the first presentation of HHT in 26% of patients with HHT and pulmonary AVMs.¹ The key to this case was that the patient had an oxygen saturation of 88% with regular heart and respiratory rates. This should raise concern for pulmonary vasculature abnormalities and 29.5% of respondents correctly selected CTA chest as an evaluation tool. Fifteen to fifty percent of patients with HHT will have pulmonary AVMs.² The additional clue of a history of spontaneous epistaxis in this patient raises specific concern for HHT and prompts imaging of the liver (selected by 7.3% of respondents) and spine (selected by 7.6% of respondents). A total of 30% to 75% of patients with HHT will have liver AVMs, although fewer than 10% will have symptomatic liver disease.³ The final correct imaging choice was lower extremity Dopplers, which are indicated to look for sources of clotting, not specific to HHT. Interestingly, the most common imaging choice selected by respondents (52%) was CTA head, which is not indicated in this case. MRI is recommended to evaluate for intracranial AVMs.⁴

The final question of this Mystery Case asked about genetic etiology. Only 15.6% of respondents identified *ENG* as the most common gene associated with HHT. *ENG*, or endoglin, causes HHT1 and accounts for about 60% of cases of HHT. A total of 34.4% of respondents selected *ACVRL1* (also known as *ALK1*), which is associated with HHT2 and is the second most common mutation, accounting for 37% of cases.³

This Mystery Case illustrates a rare but important etiology for stroke that can be identified with a thorough clinical history.

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