Clinical Reasoning:

Acute onset facial droop in a 36-year-old pregnant woman

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SECTION 1

A 36-year-old woman, G1P0, 22 weeks pregnant, presented to the emergency department for evaluation of acute onset facial droop. Her medical history included ulcerative colitis, primary sclerosing cholangitis, and heterozygosity for the prothrombin *G20210A* mutation. She was on 10,000 units of subcutaneous heparin twice daily for a previous deep vein thrombosis secondary to her prothrombin mutation; she was noncompliant with prescribed aspirin.

On examination, the patient's only neurologic deficit was complete hemiparalysis of the right face. Earlier on the day of admission, she briefly lost consciousness and urinary continence in the shower and regained awareness on the floor. She denied confusion

subsequent to this unwitnessed event. The patient also denied recent illnesses or sick contacts.

Blood pressure on admission was 129/86 mm Hg. Laboratory studies revealed a slight elevation in leukocyte count ($14.3 \times 1,000/\mu\text{L}$), but were otherwise unremarkable, including toxicology screen and coagulation studies. CT head demonstrated a 9 mm area of intraparenchymal hemorrhage in the left basal ganglia (figure 1) and the patient was admitted to the neurology intensive care unit for blood pressure control and monitoring.

Questions for consideration:

1. What are the likely etiologies of this patient's hemorrhage?
2. What further workup would you pursue?

Figure 1 CT imaging

(A) Noncontrast CT head demonstrates a 9-mm hemorrhage in the left basal ganglia (arrow). (B) Noncontrast CT head completed several hours later demonstrates bilateral areas of hypodensity in the periventricular white matter (arrow).

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Supplemental data
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SECTION 2

Stroke in pregnancy is a rare but significant cause of morbidity and mortality. Between ages 15 and 35 years, stroke is more prevalent in women than men, which is partially explained by pregnancy-related stroke.¹ Estimations of the incidence of ischemic and hemorrhagic stroke in pregnancy and the postpartum period vary; for instance, the reported incidence of hemorrhagic stroke in pregnancy ranges from 3.8 to 18.1 per 100,000 deliveries.² Intracerebral hemorrhage (ICH) risk appears to be greatest in the peripartum and postpartum period, likely secondary to rapid shifts in hemodynamics and coagulability.^{1–3} Hemorrhagic stroke has a higher mortality rate than ischemic stroke in pregnancy and the puerperium.^{2,4}

In the pregnant population, ICH is most commonly a result of aneurysm rupture, arteriovenous malformation (AVM), hypertensive disease, or cerebral venous thrombus. Several studies have reported vascular anomalies as the most common etiology of ICH in pregnancy.^{1,5} Although the changed hemodynamics of pregnancy, including increased blood volume and venous blood pressure, suggest increased risk of aneurysmal rupture or AVM bleeding, the literature is divided on whether this theoretical risk manifests clinically.^{2,4} Cavernous malformations may enlarge, but are not a high-flow system (unlike AVMs), and have not shown increased risk of bleeding.⁵

Ischemic stroke etiologies include those common in the nonpregnant population: cardioembolic, artery-to-artery thromboembolism, arterial dissection, and hypercoagulable disorders.⁴ Preeclampsia

and eclampsia are important risk factors for both ischemic and hemorrhagic stroke.^{2,3}

Regarding risk factors of intracranial hemorrhage specifically, one large study, using a representative sample of the US obstetrical population via the Nationwide Inpatient Sample, identified advanced maternal age (>35 years), hypertensive disease in pregnancy (including preeclampsia and eclampsia), coagulopathy, African American race, and tobacco use as risk factors.² Other etiologies of ICH include disseminated intravascular coagulation, coagulopathies, Moyamoya disease, neoplasms, drug use, and trauma.

In our patient, there was concern for spontaneous hemorrhage secondary to her anticoagulation. Reversal was not attempted as the etiology of the hemorrhage was unclear and, given the patient's prothrombin gene heterozygosity, the risks outweighed the benefits. Platelet counts never fell below normal limits, and a platelet function assay was unremarkable.

Approximately 8 hours after symptom onset, the patient's mental status abruptly changed. She had word-finding difficulty and could no longer name low-frequency words, but was able to follow commands. She had subtle signs of right-sided weakness. Repeat CT head demonstrated a new hypodensity on the right (figure 1).

Question for consideration:

1. What investigatory studies are appropriate at this time?

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SECTION 3

With the patient's change in examination, MRI brain as well as vascular imaging should be obtained as rapidly as possible. With bilateral infarcts in a patient with hypercoagulable risk factors, venous thrombosis is also on the differential. Venous thrombosis itself can result in hemorrhage and ischemic infarcts resulting from venous thrombus are prone to hemorrhagic transformation.

Figure 2 MRI, magnetic resonance angiography, and magnetic resonance venography imaging

(A) Diffusion-weighted imaging demonstrates area of hyperintense diffusion restriction in the R frontal lobe (arrow) as well as bilateral heterogeneous areas of signal change. (B) Apparent diffusion coefficient image with hypointensity in the same area. (C) Fluid-attenuated inversion recovery (FLAIR) image demonstrates diffuse edema and bilateral areas of hyperintensity in the basal ganglia, corpus callosum, and subcortical white matter. (D) Susceptibility-weighted imaging with hypointensity in multiple areas, corresponding with the regions of increased FLAIR signal in C, suggests hemorrhagic changes in those areas.

A lumbar puncture should be performed afterwards as long as there is no contraindication (i.e., concern for herniation).

The patient's condition continued to rapidly deteriorate. She became obtunded, unable to follow commands or produce speech, and required intubation for airway protection. Cranial nerve deficits included bilateral exotropias, downward deviation of the left eye, and no blink to threat bilaterally. On motor examination, she withdrew to noxious stimulation in all extremities with less spontaneous movement on the right. MRI, magnetic resonance angiography, and magnetic resonance venography of the brain demonstrated no vascular anomalies but revealed multifocal areas of restricted diffusion in the bifrontal subcortical white matter, brainstem, bilateral basal ganglia, and right parietal cortex, associated with T2 hyperintensity and edema, and hemorrhage on susceptibility-weighted sequences (figure 2). These lesions were primarily in the periventricular white matter. At our institution, pregnancy is an absolute contraindication to contrast administration.

CSF results showed 110/ μ L erythrocytes, 4/ μ L nucleated cells, 52 mg/dL protein, and 56 mg/dL glucose. Oligoclonal bands, Epstein-Barr virus (EBV), herpes simplex virus (HSV), varicella-zoster virus, cytomegalovirus, venereal disease research laboratory, Lyme, and an arbovirus panel (including West Nile, St. Louis encephalitis, California encephalitis, Eastern and Western equine encephalitis immunoglobulin G and immunoglobulin M antibodies) in the CSF and serum HIV were negative. Influenza was not tested.

The following day, repeat CT head demonstrated worsening hemorrhages and expansion of the surrounding edema. An intracranial pressure monitor was placed and mannitol and hypertonic saline started.

Questions for consideration:

1. What is the differential diagnosis?
2. What are the options for treatment?

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SECTION 4

The patient's rapid deterioration and the presence of multifocal, hemorrhagic, and diffusion restricting lesions on MRI suggested an inflammatory or infectious etiology. Infectious causes include HSV, West Nile virus and other viral infections, infectious endocarditis, fungal infections, particularly aspergillosis, or mycobacterial agents such as tuberculosis. Her MRI was suggestive of a fulminant demyelinating process: acute hemorrhagic leukoencephalitis (AHLE), also known as Weston-Hurst syndrome (figure 2 and figure e-1 at Neurology.org). Acute necrotizing encephalitis (ANE) was also a consideration; however, the patient had no antecedent febrile illness and her imaging was inconsistent with the characteristic symmetric hemorrhagic necrosis of the thalami seen in ANE.⁶ Her fall in the shower was ultimately attributed to possible seizure, and continuous EEG demonstrated diffuse background slowing but no epileptiform discharges. The lower motor neuron–type facial droop has a few possible explanations. The patient had bilateral injury to her motor tracts as evidenced on her second CT scan and MRI, which may have injured the innervation to the forehead. Another explanation is inflammation of the seventh nerve, although a concomitant Bell palsy is unlikely. Finally, it is possible that the patient had an upper motor presentation that was misinterpreted.

Given the patient's rapid decline, we pursued aggressive measures. Treatment with 1 g of methylprednisolone IV daily and empiric treatment of HSV encephalitis with acyclovir were initiated. Acyclovir was subsequently discontinued when her HSV PCR returned negative. Central access was obtained and plasma exchange emergently initiated on the night of admission. The patient showed no improvement with immunosuppression. She received 4 days of high-dose IV steroids and 3 sessions of plasma exchange.

Repeat imaging demonstrated progressive cerebral edema. Further immunosuppression with rituximab or cyclophosphamide and neurosurgical intervention were ultimately declined by the patient's family. Fetal ultrasound was unremarkable. Maternal–fetal medicine was consulted, and discussed with family that delivery or resuscitation at 22 weeks is not recommended given the low survival rates and high risk of neurodevelopmental complications. On hospital day 5, given the patient's poor response to treatment, the overall poor prognosis, and the unknown prognosis of the patient's fetus, the family determined that the patient would not have wanted life-supporting therapies in this situation and patient care was transitioned to comfort measures. The patient's family declined fetal resuscitation. Prolonging life support to increase gestational time was also declined. The

patient was extubated and died 4 hours later. The family declined autopsy.

DISCUSSION Without autopsy or brain biopsy, a definitive diagnosis was not possible. However, our patient's rapid progression of symptoms and imaging findings are suggestive of AHLE. AHLE is a highly aggressive variant of acute disseminated encephalomyelitis (ADEM). Like ADEM, it frequently presents in young children (<10 years old) after an infectious trigger; however, AHLE has rapid worsening of neurologic symptoms with hemorrhage and edema, which can result in herniation and death.⁷ Autopsy studies have demonstrated involvement of both white and gray matter.⁸

ANE, another rare and often fatal disease that most commonly affects children, should also be considered. Some authors conflate ANE and AHLE,⁹ and both are associated with similar infections; however, hemorrhage is not seen in the white matter in ANE. Pathology shows an absence of inflammatory cells in the affected parenchyma.⁶

The definitive pathophysiology of AHLE is unknown, although HSV, EBV, and mycoplasma infections are reported disease triggers.⁹ Our patient's CSF was negative for HSV and EBV; however, mycoplasma was not tested. A small number of patients have developed AHLE as a result of partial complement factor I deficiency; levels were normal in our case.⁹

The patient's unremarkable lumbar puncture was likely a result of the test being performed early in the disease course. Expected CSF findings include pleocytosis with neutrophilic predominance as well as elevated protein, erythrocyte, and lymphocyte counts.⁷

The characteristic pathologic findings include hemorrhagic necrosis with perivascular demyelination and fibrinoid necrosis of the blood vessel walls.⁹ Our patient's history of ulcerative colitis may have altered her risk of AHLE as having one autoimmune disorder puts patients at increased risk of additional autoimmune processes.

Although AHLE is largely fatal, uncommon cases of successful treatment have been reported.¹⁰ Early diagnosis and treatment is paramount; treatment options include immunosuppression with high-dose steroids, cyclophosphamide, plasmapheresis, and management of elevated intracranial pressure. AHLE is a rapidly progressive, devastating disease. Awareness is important, as aggressive and early treatment with immunosuppression gives patients their best chance for survival.

AUTHOR CONTRIBUTIONS

Dr. George: manuscript preparation, care of patient. Dr. Youn: manuscript revision, care of patient. Dr. Marcolini: manuscript revision, care of patient. Dr. Greer: manuscript revision, care of patient.

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