A SELF-TEST

IM BOARD REVIEW JAMES K. STOLLER, MD, EDITOR

ON A CLINICAL CASE

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A hypertensive emergency in an obese young woman

31-YEAR-OLD WHITE WOMAN presents to the emergency room of another hospital complaining of severe headache, swelling of the face and limbs, and abdominal pain lasting 2 days. While there she suffers several generalized tonic-clonic seizures, which are controlled with intravenous (IV) lorazepam.

Her blood pressure is markedly elevated at 235/114 mm Hg, and she is diagnosed as having a hypertensive emergency. Several IV doses of labetalol are given without significant response, but her blood pressure responds to IV nitroprusside. Once stabilized, she is transferred to our hospital and admitted to the intensive care unit.

She has:

- New seizures
- Headache
- BP 235/114
- Weight 256 lb
- Edema
- Proteinuria
- Last menstrual

period unknown She reports that she has had a severe, throbbing, continuous headache, which she rates as 7 on a scale of 10, for the past 2 days. She also has had mild nausea and vomiting, mild pain in the right upper quadrant, edema of the upper and lower extremities, and facial swelling, and all of these began about the same time as the headache. She has had no fever, chills, chest pain, paresthesias, shortness of breath, weight change, or decrease in urine output.

She has a long-standing history of obesity and markedly irregular menstrual periods. She has never been pregnant. Until this time, she was having menstrual periods approximately once a year. She cannot recall the date of her last period. She denies having hypertension or a seizure disorder or using any medications, drugs of abuse, or alcohol. She does not smoke cigarettes.

PHYSICAL EXAMINATION

The patient is awake and responsive. Her blood pressure is 192/108 mm Hg while on

nitroprusside, but with titration it decreases to approximately 170/100. Her pulse rate is 94 beats per minute, and she is afebrile. She weighs 116 kg (256 lb) and is 1.77 meters tall (5 feet 9.5 inches), for a body mass index of 37, which is classified as obese.

Head. Her pupils are midrange and reactive. There is no nystagmus, and the fundi are normal.

Chest. Lungs are clear, and there are no murmurs or additional heart sounds.

Abdomen. No distinct masses are palpated, and there is no tenderness or distension. Bowel sounds are present.

Extremities. Pulses are equal and full, and no bruits are noted. Pitting edema of 1+ is noted in all extremities.

Neurologic. Sensory and motor examinations are normal. Deep tendon reflexes are normal in the upper and lower extremities. No cranial nerve abnormalities are noted.

INITIAL TESTS

Complete blood count

- White blood cell count 14.3 × 10⁹/L (normal range 4.5–10.8)
- Hemoglobin 13.3 g/dL (12.0–16.0)
- Platelet count 140 × 10⁹/L (150–450).

Chemistry profile

- Sodium 138 mEq/L (136–145)
- Potassium 4.0 mEq/L (3.5–5.0)
- Chloride 109 mEq/L (98–110)
- Bicarbonate 23 mEq/L (22–32)
- Blood urea nitrogen 15 mg/dL (8.0–22.0)
- Creatinine 1.0 mg/dL (0.5–1.2)
- Glucose 129 mg/dL (70–110)
- Aspartate aminotransferase 75 U/L (15–46).



Urinalysis

- Blood: grossly positive
- Bilirubin negative
- Moderate leukocytes
- Negative nitrites
- Protein \geq 300 mg/dL
- Bacteria 4+
- White blood cells 25 to 50 per highpower field
- Epithelial cells 5 to 10 per high-power field.

Other tests

- Electrocardiography: normal sinus rhythm without changes in ST or T waves
- Toxicology screen: negative for drugs of abuse.

DIFFERENTIAL DIAGNOSIS

- **1** Which is the most likely cause of this patient's findings?
- Drug abuse
- □ Fibromuscular dysplasia
- Abrupt cessation of antihypertensive therapy
- Eclampsia
- □ Atherosclerotic renal artery stenosis
- Pheochromocytoma

Hypertensive crises occur in about 1% to 2% of patients with established hypertension, many of whom were prescribed therapy but whose hypertension remains uncontrolled.1 Hypertensive crises include hypertensive emergencies and urgencies. Although no set blood pressure constitutes a crisis, markedly elevated blood pressures (eg, > 220/140 mm Hg) and progressive damage of target organs (brain, eyes, kidneys, heart) typify hypertensive emergencies and require immediate attention and blood pressure reduction. Patients with a hypertensive urgency typically have blood pressure elevations that are less severe and have no evidence of progressive organ damage; these patients require blood pressure reduction within a few hours.²

Crises occur more frequently among men, African Americans, and the elderly. The factors leading to the severe and rapid elevation of blood pressure during a crisis are poorly understood. The release of humoral vasoconstrictive

TABLE 1

Some common causes of hypertensive emergency

Acute left ventricular failure Acute renal failure Aortic dissection Catecholamine excess: rebound hypertension, pheochromocytoma Cerebrovascular accident or intracerebral hemorrhage Drug abuse Eclampsia Hypertensive encephalopathy Myocardial infarction Vasculitides

substances from the stressed vessel wall is thought to be responsible for the initiation and perpetuation of the hypertensive crisis.³

This patient presented with markedly elevated blood pressure and new-onset seizures. The diagnosis of hypertensive emergency made at the outlying hospital appears correct, although the underlying cause is not readily apparent. The differential diagnosis of hypertensive emergency is extensive. **TABLE 1** lists some of the more common causes. In this case, clues from the history helped to narrow the differential diagnosis.

Drug abuse

Cocaine, amphetamines, and other drugs of abuse can cause severe hypertension and seizures, but they should be identified with urine and serum toxicological screens. However, if a large exposure occurs rapidly, such as occurs in "body packing" when an ingested packet of drug bursts or leaks inside the gastrointestinal tract, the urine screen may initially be negative (personal observation, L.M.K.).

Fibromuscular dysplasia

This disease usually affects women, usually between the ages of 30 and 50. It is a nonatherosclerotic, noninflammatory vascular disease of unknown cause.⁴ Patients would be expected to present with a history of preexisting hypertension, but seizures would be unexpected. Even so, this unlikely cause may still be possible in this young woman.

A history of irregular menses does not rule out pregnancy

TABLE 2

Diagnosis of preeclampsia and severe preeclampsia: Working Group criteria

Preeclampsia*

- A systolic blood pressure of 140 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher occurring after 20 weeks of gestation in a woman whose blood pressure has previously been normal
- Proteinuria, with excretion of 0.3 g or more of protein in a 24hour urine specimen

Severe preeclampsia

- A systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 110 mm Hg or higher on two occasions 6 or more hours apart in a pregnant woman who is on bed rest
- Proteinuria with excretion of 5 g or more of protein in a 24-hour urine specimen or a dipstick reading of 3+ or greater on two random samples collected 4 or more hours apart
- Oliguria, with excretion of less than 500 mL of urine in 24 hours

Pulmonary edema or cyanosis

Impairment of liver function

Visual or cerebral disturbances

Pain in the epigastric area of right upper quadrant

Decreased platelet count

Intrauterine growth restriction

*A woman with preeclampsia who has new-onset grand mal seizures is considered to have eclampsia

BASED ON THE REPORT OF THE NATIONAL HIGH BLOOD PRESSURE EDUCATION PROGRAM WORKING GROUP ON HIGH BLOOD PRESSURE IN PREGNANCY. AM J OBSTET GYNECOL 2000; 183(SUPPL):1–22.

Abrupt cessation of antihypertensive therapy

Withdrawal from antihypertensive drugs (eg, clonidine, beta-blockers) can cause severe rebound hypertension. Our patient had not previously been treated for hypertension and denies taking medications.

Eclampsia

Preeclampsia is characterized by hypertension, edema, and proteinuria occurring after 20 weeks of gestation in a previously normotensive patient (TABLE 2).⁵ About 5% to 7% of all pregnancies (ie, 200,000 women in the United States each year) are affected.⁶

Our patient has marked blood pressure

elevations, new-onset seizures, peripheral edema, and proteinuria—findings consistent with eclampsia. Pregnancy and related complications must be considered in a patient of childbearing potential with this presentation. Pregnancy by itself is physiologically a hypotensive condition, but blood pressures can be markedly elevated when complicated by toxemia. Such patients can present in a state of hypertensive urgency or emergency.

Atherosclerotic renal arterial stenosis

The prevalence of atherosclerotic renal arterial stenosis increases with age. Many patients have underlying essential hypertension with superimposed malignant hypertension due to the stenosis. It is often associated with other atherosclerotic disease, diabetes, and smoking.⁷ This would be an uncommon problem in a younger patient such as ours who does not smoke.

Pheochromocytoma

Pheochromocytoma is rare, with an incidence rate of 0.5 to 0.8 per 100,000 person-years. It is a chromaffin tissue tumor of adrenal and extra-adrenal sites that produces excess catecholamines. The classic presentation is headache, sweating, palpitations, trembling, and anxiety, all of which may be paroxysmal.⁸ Ten percent of pheochromocytomas are malignant, and about 25% are familial.⁹ Pheochromocytomas may be responsible for 0.3% to 1.9% of cases of secondary hypertension.¹⁰

Our patient has no history of hypertension, headaches, or palpitations, so although pheochromocytoma is still a consideration, other more likely causes should be sought.

CASE CONTINUED

The patient has no further seizures and continues on IV nitroprusside, which controls her blood pressure adequately. A urine pregnancy test performed on arrival at our hospital is positive and is confirmed by testing for serum beta human chorionic gonadotropin (17,000 IU/L; normal < 3).

Although not likely in this case, a spuriously negative urine test result in the first hospital emergency room may have led the treat-

HYPERTENSIVE EMERGENCY BIYYANI AND COLLEAGURES

ing team away from further consideration of a pregnancy-related complication, and one could argue that when a pregnancy-related complication is suspected, a serum test is warranted. Given the positive pregnancy test result at our hospital, eclampsia is considered the most likely cause of her symptoms.

2 Which of the following should be part of the patient's management at this point?

- Obtain emergency bedside ultrasonography of the abdomen
- □ Change the blood pressure treatment to IV labetalol
- Change the blood pressure treatment to IV hydralazine
- □ Start IV magnesium sulfate
- □ Obtain an emergency obstetrical consult
- $\Box \quad \text{All of the above}$

All of the above are correct interventions.

Ultrasonography to look for pregnancy is critically important if pregnancy is likely and if life-threatening complications could occur. A diagnosis of pregnancy opens an array of differential diagnoses. Furthermore, all subsequent management must focus on fetal condition and best interest.

Our patient undergoes ultrasonography, which reveals a gravid uterus; the fetus is estimated to be at 28 weeks of gestation. The ultrasonogram shows low amniotic fluid and reduced fetal activity, which are causes for concern.

Treating hypertensive emergency in pregnancy

The treatment of eclampsia-related hypertensive emergency differs from that of hypertensive emergency due to other causes and must be considered early to minimize the risk of harm to both the patient and the fetus. In addition, the syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP) is an atypical, acute form of toxemia that can present with right upper quadrant pain, nausea, and emesis. It needs to be recognized early in an expectant mother as it can lead to hepatic rupture.¹¹

To maintain adequate placental blood flow, a systolic blood pressure of 140 to 155 mm Hg and a diastolic blood pressure of 90 to 100 mm Hg should be maintained.^{12,13} Hypotension must be avoided because it disrupts placental blood flow, and in toxemia, placental function may be exceptionally vulnerable and intolerant of iatrogenic hypotension. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are contraindicated because they can adversely affect fetal development, particularly in the second and third trimesters. Therefore, they are not to be used to treat preexisting hypertension or hypertensive emergencies when there is a possibility that the patient is pregnant.

Sodium nitroprusside is commonly used to treat hypertensive crisis, but it should not be used in eclampsia, owing to the risk of cyanide toxicity to the fetus during protracted therapy.

Intravenous hydralazine is a direct arteriolar vasodilator that causes sympathetic stimulation of baroreceptors, increases heart rate, increases cardiac output, and thus helps to preserve placental blood flow.¹⁴ Overtreatment with hydralazine leading to hypotension is not uncommon, however, especially when it is given concomitantly with magnesium sulfate, as both drugs act by inhibiting the cellular influx of calcium.

Labetalol is a combined alpha-1, beta-1, and beta-2 blocking agent that has recently gained popularity in this situation.⁵ When it is given IV, its effect on beta receptors in the peripheral arterial smooth muscle is six times as great as its effect on alpha receptors.¹⁵ However, the predominantly beta-blocker effect on the fetus in an acute setting is not a concern and serves maternal-fetal interests well because the dosage can be titrated from minute to minute. This rapid response is in contrast to that of IV hydralazine, which can have a 20-minute or longer delay in onset.

Selective intravenous beta-blockers should not be used because of adverse effects on uteroplacental and fetal hemodynamics.¹³

The treatment of choice, either labetalol or hydralazine, is not clear, and evidence supporting the use of one over the other is limited.⁵ Thus, either labetalol or hydralazine could be used in this patient.

Magnesium sulfate is effective in preventing convulsions and recurrent seizures in primary eclampsia. Magnesium levels should be checked every 4 to 6 hours, and the infusion rate should be adjusted to maintain a therapeutic blood level of 4 to 6 mEq/L. Urinary output should be checked hourly, and the patient should be assessed for signs of magnesium toxicity, such as loss of ankle tendon reflexes, the earliest sign. Adverse effects can be reversed with calcium gluconate. Magnesium sulfate infusion should be continued until symptoms resolve and diuresis begins. Diuresis, with urinary output of more than 100 to 200 mL per hour, typically occurs within 24 to 48 hours postpartum. The mechanism of the diuresis is unknown but may be related to resolution of the underlying preeclampsia after delivery.

An emergency obstetrical consult should be obtained to plan for definitive treatment.

New insights into how preeclampsia develops

Recent work has brought much insight into the development of preeclampsia.

Placental ischemia is an early event contributing to the production of soluble factors leading to endothelial dysfunction.¹⁶ The resulting imbalance between proangiogenic and antiangiogenic factors may then lead to intrauterine growth retardation and preeclampsia.

Normally, vascular endothelial growth factor (VEGF) and placental growth factor (PGF), both of which are proangiogenic factors, are expressed at high levels during the early part of pregnancy, resulting in placental angiogenesis and an increase in placental mass.⁶

A major endogenous inhibitor of angiogenesis, soluble fms-like tyrosine kinase 1 (sFlt-1), is produced in abundant quantities towards the end of pregnancy.¹⁷ It is a soluble version of the VEGF receptor generated by alternative splicing of the Flt-1 gene product, leading to a truncated extracellular domain that retains the ability to bind to VEGF and PGF and thereby regulates normal placentation.⁶ Preeclampsia is associated with overproduction of sFlt-1, which in turn binds VEGF and PGF, preventing them from binding to cell surface receptors and leading to endothelial dysfunction.⁶

The excess production of sFlt-1 in preeclamptic patients has been confirmed

using gene expression profiling and microarray chip studies, which showed an increase in messenger RNA for sFlt-1.¹⁸ Gene transfer of sFlt-1 using an adenoviral vector into pregnant rats produced hypertension, proteinuria, and glomerular endotheliosis, the classic pathologic lesion of preeclampsia.¹⁸

Work continues to define the role of proangiogenic and antiangiogenic factors in placental development and preeclampsia.

CASE CONTINUED

The patient's therapy is changed from IV nitroprusside to IV labetalol and IV magnesium sulfate, and she remains free of seizures.

3 Which is the definitive treatment for this patient?

- □ Bed rest in the left lateral position
- □ Termination of pregnancy
- □ High-protein diet
- Daily aspirin

The definitive cure for preeclampsia is termination of pregnancy. Except in unusual circumstances, delivery is mandated once eclampsia has occurred. Vaginal delivery can be attempted if the patient has already been in active labor, if the cervix is favorable, and if the patient is clinically stable.¹⁹ The rapidity with which delivery must be achieved depends on the status of the mother and the fetus after the seizure and on the availability of laboratory data on the patient.

Bed rest in the left lateral position during an eclamptic seizure decreases the incidence of aspiration and improves placental perfusion.

Aside from delivery, there is no treatment for preeclampsia. In cases of severe preeclampsia remote from term, one can consider expectant pregnancy management and treating the fetus transplacentally with antenatal steroids to reduce the risks of prematurity. This may improve neonatal outcome, but maternal-fetal stability is an essential prerequisite. Eclampsia, a complication of severe preeclampsia, describes an unstable maternal-fetal condition deserving of delivery, with delay warranted only to stabilize the mother's condition.

In pregnancy avoid:

- ACE
 inhibitors
- ARBs
- Selective IV beta-blockers
- Nitroprusside

Daily aspirin and a high-protein diet have no role in the treatment of patients with eclampsia.

PREVENTING PREECLAMPSIA FROM PROGRESSING TO ECLAMPSIA

Convulsions in eclampsia

Although the pathogenesis of eclamptic convulsions remains unknown, cerebral imaging suggests that abnormalities in eclampsia (mostly vasogenic edema) are not unlike those seen in hypertensive encephalopathy. The onset of eclamptic convulsions can be antepartum (38% to 53%), intrapartum (18% to 36%), or postpartum (11% to 44%).²⁰ Unfortunately, except for early detection of preeclampsia and close vigilance, no reliable tests or symptoms predict the development of eclampsia.

Magnesium sulfate is the treatment of choice

The definitive

preeclampsia

is termination

of pregnancy

cure for

Magnesium sulfate is the drug of choice for reducing the rate of eclampsia developing intrapartum and immediately postpartum. In four large randomized trials comparing magnesium sulfate vs no treatment or placebo in patients with severe preeclampsia,^{21–24} the rate of eclampsia was significantly lower in those assigned to receive magnesium sulfate (0.6% vs 2.0%, relative risk 0.39, 95% confidence interval 0.28–0.55). An estimated 71 women would need to be treated to prevent one case of eclampsia.

Magnesium sulfate also prevents recurrent seizures in those who have already developed eclampsia.

The Collaborative Eclampsia trial²⁵ compared standard anticonvulsant regimens in 1,687 women with eclampsia. Data were available for 453 patients randomized to receive magnesium sulfate vs 452 receiving diazepam, and for 388 randomized to receive magnesium sulfate vs 387 receiving phenytoin. Women receiving magnesium sulfate had a 67% lower risk of recurrent convulsions than those receiving phenytoin and a 52% lower risk than those receiving diazepam. Although rates of maternal death were not significantly lower among women taking magnesium sulfate, these women were less likely to require artificial ventilation than those taking phenytoin.

Risk from previous eclampsia

Women with a history of eclampsia are at increased risk of eclampsia (1% to 2%) and preeclampsia (22% to 35%) in subsequent pregnancies.^{26–30} Once preeclampsia is diagnosed, the condition should be monitored closely, since the clinical condition may change acutely and, if not appropriately attended to, may lead to serious complications, such as eclampsia.

CASE CONCLUDED

Our patient's pregnancy is at only 28 weeks and her cervix is unfavorable for delivery, so safe induction of labor and vaginal delivery are not anticipated. Cesarean section is performed, and a healthy, vigorous 28-week infant is delivered. The neonatal course is free of any major complications other than the anticipated respiratory distress syndrome.

TAKE-HOME POINTS

Several features of our patient's case deserve attention:

•In an obese patient, a nonrevealing physical examination may argue for an early resort to imaging to identify pregnancy, if this is suspected.

•A history of irregular menses does not rule out pregnancy.

• It is important to obtain urine and serum pregnancy tests before instituting therapy in such situations.

•Because many pregnancies are unintended and unsuspected, denial of pregnancy by the patient is of limited value.

•Toxemia deserves to be high in the differential diagnosis for women of reproductive age presenting in hypertensive crisis, in view of the life-threatening complications that can occur from an inadequately attended toxemia.

Interestingly, our patient was completely unaware of her pregnancy and had been told previously that she would not be able to conceive. Because of her body habitus, the gravid uterus was not noted on physical examination. A urine pregnancy test was not obtained at the outlying institution, and therefore the patient received a diagnosis of hypertensive emergency and was treated with nitroprusside, which if used for an extensive period could have led to the death of the fetus. Also, failure to diagnose preeclampsia-eclampsia early in our patient resulted in hypertensive emergency and eclamptic seizures. Fortunately, the diagnosis was made before any other complications of eclampsia occurred, such as cerebral hemorrhage, abruptio placenta with disseminated intravascular coagulopathy, pulmonary edema, renal failure, or liver hemorrhage any of which could have resulted in the death of the fetus or the patient.

ACKNOWLEDGMENTS: We wish to thank Ronald D. Perrone, MD, Associate Chief, Division of Nephrology and Medical Director of the Kidney Transplant Program, Tufts-New England Medical Center, and Frederick C. Whittier, MD, Professor of Medicine, Northeastern Ohio Universities College of Medicine, for their helpful comments.

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