A 19-year-old female completed her first ever pregnancy without complication. On the fourth postpartum day, she abruptly developed a severe and unremitting headache while sitting at home. At the time of her evaluation 6 hours later, her headache persisted and was described as severe ("the worst of my life"), diffuse, nonlateralized, nonpulsatile, and not affected by positional change. She denied associated neck stiffness. Her past medical history was notable for episodic migraine with and without visual aura since age 11. During her pregnancy, she had experienced only occasional and relatively mild headaches.

Vital signs were stable. Blood pressure was 130/78, heart rate was 76 beats per minute, and she was afebrile. Her general and neurologic examinations were normal. Her neck was supple and there was no evidence of papilledema.

Noncontrast brain CT was performed 6 hours following headache onset and was normal. Lumbar puncture was performed and demonstrated an elevated opening pressure (320 mm/H2O); the CSF obtained was rust colored, and laboratory analyses demonstrated 250 000 RBC/mm³, 255 WBC/mm³ (80% polys, 20% mononuclear cells), glucose 77 mg/dL, and protein 185 mg/dL. Brain MRI demonstrated findings suggestive of acute thrombosis within the superior sagittal sinus, and on MRV the distal two-thirds of the sinus was not visualized.

What are the major diagnostic considerations in patients experiencing postpartum thunderclap headache? What is the most reliable and efficient means of evaluating such a patient? How should this patient be managed at this point?

EXPERT OPINION

Headache is a frequent symptom of the early postpartum period. In one prospective study, 39% of mothers experienced a headache by the end of the first postpartum week, the majority between days 4 and 6 postpartum.1 Several factors increase the likelihood of headache during the postpartum period including a current or previous history of migraine (particularly menstrual migraine), and a prior history of headache during puerperium.1 Significant neuroendocrine changes occur during the puerperium, specifically a rapid fall in circulating levels of estrogen and progesterone, and this may influence the occurrence of headache, particularly migraine.2 Migraine attacks begin for the first time during the first month postpartum in up to 5% of migraineurs.3

While postpartum headache is common, a headache that is new or different in character, especially if sudden in onset or associated with systemic or neurologic symptoms, requires immediate and careful attention (see Table). For the patient with thunderclap headache, it is important to exclude subarachnoid hemorrhage, meningoencephalitis, and arterial dissection; however, special attention is also required to investigate for the secondary causes that occur more frequently during the puerperium. These include CSF hypovolemia, cerebral venous sinus thrombosis, pre-eclampsia/eclampsia, posterior leukoencephalopathy.
syndrome (PLES), postpartum cerebral angiopathy, pituitary apoplexy, Sheehan’s syndrome, lymphocytic hypophysitis, and ischemic and hemorrhagic stroke.

Postdural puncture headache (PDPH) is an important cause of headache in postpartum patients. In the obstetrical setting, the two most frequently utilized techniques for analgesia and anesthesia are spinal and epidural procedures. Data from a recent meta-analysis revealed that parturients have a 1.5% risk of accidental dural puncture with epidural insertion; of these, 52% developed PDPH secondary to a persistent leak and CSF hypovolemia. With combined spinal and epidural procedures, PDPH has been reported to occur in up to 8.6% of patients. The likelihood of PDPH after inadvertent dural puncture is increased by pushing during the second stage of labor and the cumulative duration of bearing down. While the headache may begin as early as day 1, the majority of PDPH develop later during the first week when the mother is at home and ambulatory. PDPH may present as an acute or subacute headache, or as an indolent and progressive headache without obvious postural features.

The 2004 International Classification of Headache Disorders, Second Edition, now recognizes that headache attributable to pre-eclampsia (10.3.4) and headache attributable to eclampsia (10.3.5) may develop either antepartum, at the time of delivery, or during the postpartum period. Advances in obstetrical care have decreased the frequency of pre-eclampsia/eclampsia; however, up to 50% of cases develop postpartum and often begin after discharge from hospital. In postpartum (late)
precipitating more severe vasospasm and cerebral infarction. Appropriate treatment is unknown although calcium channel antagonists and steroids have been advocated.\textsuperscript{14}

Pituitary apoplexy, a rare but potentially life-threatening condition due to infarction or hemorrhage of the pituitary gland, should be considered in all postpartum women with thunderclap headache. During pregnancy, the normal pituitary gland enlarges predominately due to estrogen-stimulated hyperplasia and hypertrophy of prolactin-producing lactotropes.\textsuperscript{15} These hormonal changes can also have a significant stimulatory effect on pituitary macroadenomas, particularly during the final trimester.\textsuperscript{15} Hemorrhage into the pituitary gland (typically into a pituitary macroadenoma) can present with acute onset headache with or without associated vomiting, visual changes, oculomotor paresis, fever, alterations in consciousness, and/or pituitary hypofunction. In contrast, Sheehan’s syndrome refers to infarction and necrosis of a nontumorous pituitary gland.\textsuperscript{16} Pituitary hypertrophy may render the highly vascularized pituitary susceptible to vascular compromise and correspondingly, Sheehan’s syndrome occurs in the setting of significant peri- or postpartum hypotension or hemorrhage.\textsuperscript{16} It is now extremely uncommon due to advances in obstetric care. Finally, lymphocytic hypophysitis, an autoimmune inflammation of the pituitary gland, can present with an acute-onset headache or more commonly as a subacute or chronic headache with visual disturbances and symptoms of hypopituitarism.\textsuperscript{17,18} Lymphocytic hypophysitis is rare, but is more common during pregnancy, particularly during the final trimester or postpartum period. Pituitary apoplexy may be misdiagnosed as subarachnoid hemorrhage or meningoencephalitis because of the presence of leukocytes and erythrocytes in the cerebrospinal fluid.\textsuperscript{19} MRI is superior to CT for imaging the pituitary gland and for distinguishing between pituitary inflammation, infarction, and hemorrhage. Rapid diagnosis allows for appropriate endocrine or neurosurgical management, when indicated.

Stroke, both ischemic and hemorrhagic, occurs with increased frequency during the postpartum period.\textsuperscript{20,21} Using sex-, age-, and parity-matched controls for 654,957 women (representing over 1 million deliveries between 1987 and 1995) from the nationwide Swedish cohort, Salonen and colleagues determined the relative risks of stroke by subtype around the time of delivery (2 days before to 1 day after delivery) and in the postpartum period (2 days to 6 weeks postdelivery).\textsuperscript{21} The relative risk of cerebral venous thrombosis (CVT) around delivery was 115, subarachnoid hemorrhage 47, intracerebral hemorrhage 95, and cerebral infarction 34; during the postpartum period, relative risks fell but remained elevated in all groups—venous thrombosis 15, subarachnoid hemorrhage 2, intracerebral hemorrhage 12, and cerebral infarction 8. While pre-eclampsia/eclampsia, PLES, PPCA, and cerebral venous sinus thrombosis contribute to the increased likelihood of stroke, arterial occlusion has been reported to be more common (secondary to cardiac emboli, coagulopathies, and carotid artery dissection).\textsuperscript{22} Other unique causes of stroke in the postpartum period include amniotic fluid embolism and hemorrhagic metastatic choriocarcinoma. Headache, particularly thunderclap headache, may be the only or the main presenting symptom for both ischemic and hemorrhagic stroke.

Cerebral venous thrombosis may result from partial or complete obstruction of the major venous sinuses, superficial cortical veins, or the deep venous system.\textsuperscript{23} As noted above, CVT is more common during pregnancy, particularly in the puerperium.\textsuperscript{24} While the clinical course and evolution of CVT is usually slow and indolent; overall, a thunderclap presentation occurs in up to 10% and is an even more common presentation during puerperium.\textsuperscript{24,25} Headache is usually the earliest symptom of CVT and may be the only symptom. Unfortunately, when headache is the only presenting symptom, accurate diagnosis is often delayed with potentially devastating consequences.\textsuperscript{23} CVT is important to recognize and treat early because of the potential for substantial morbidity and death in up to 10% of patients. Headache in CVT may be caused by distension of the pain sensitive cortical veins and dural venous sinuses, increased intracranial pressure, infarction, or intraparenchymal or subarachnoid bleeding. Clinical index of suspicion is elevated in the presence of signs of elevated intracranial pressure (papilledema, sixth nerve palsy), decreased alertness, focal neurologic signs, or seizures. Noncontrast CT
may be normal in up to 40% of patients with CVT, but may demonstrate hemorrhagic or nonhemorrhagic venous infarcts, hypodensity consistent with focal or diffuse brain edema, and/or a focus of hyperdensity within the occluded sinus/vein. Contrast-enhanced CT may reveal the empty delta sign—a bright triangle surrounding a central hypodense core (typically in the sagittal sinus) reflecting contrast enhancement of the dilated collateral veins and sinus walls surrounding a nonenhancing thrombus. MRI may reveal an absent flow void in the venous system and thrombi may be detected. Enhanced detection and evaluation of CVT is provided by magnetic resonance venogram (MRV).

Patients with postpartum thunderclap headache should be investigated expeditiously and carefully as the headache may herald systemic or neurologic deterioration. Evidence for pre-eclampsia (hypertension, proteinuria) should be sought. A noncontrast CT is the first imaging modality of choice. If normal or non-diagnostic, MRI should be obtained. If the patient has had spinal or epidural anesthesia, a gadolinium-enhanced MRI should be obtained to assess for evidence of pachymeningeal thickening and enhancement related to CSF hypovolemia. MRV should be included in all cases to rule out CVT. MRA of the head and neck should be considered if arterial dissection is suspected. If the MRI suggests PLES or PPCA, MRI should be added to search for multifocal segmental arterial narrowing. Lumbar puncture should be obtained when a CNS infection or subarachnoid hemorrhage is suspected. In postpartum thunderclap headache, clinicians must rule out each of the secondary causes. Specifically, several case reports highlight the diagnostic confusion when headache is attributed to inadvertent dural puncture without complete investigation.26-28

In this particular case, lumbar puncture demonstrated an elevated opening pressure (320 mm/H2O), the CSF obtained was rust colored, and contained 250,000 RBC/mm3, 255 WBC/mm3 (80% polys, 20% mononuclear cells). This CSF profile is consistent with subarachnoid hemorrhage, intraparenchymal hemorrhage with subarachnoid extension, and CVT. The brain MRI findings were suggestive of acute thrombosis within the superior sagittal sinus. This was confirmed with MRV. Anticoagulation for CVT, even in the presence of small hemorrhage, is the treatment of choice (usually intravenous heparin followed by coumadin) as it has been associated with reduction in death and dependency.29 Anticoagulant therapy is indicated for a minimum of 3–6 months. While the postpartum period increases the risk of CVT, other contributing factors should be sought including inherited thrombophilias, lupus anticoagulant, and antiphospholipid antibodies.30 The oral contraceptive pill should be avoided in future. Consideration may be given to CVT prophylaxis with low-molecular-weight heparin during subsequent postpartum periods.

REFERENCES