Chapter 8

The Engineer with Sudden Headache

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Case History

A 63-year-old aviation engineer presented to the emergency department with a 6-day history of a unilateral right-sided headache. The headache began suddenly while he was eating dinner. The headache was unilateral, severe, throbbing in quality, and associated with nausea and recurrent bouts of emesis. He had his blood pressure taken at a local fire department and was told that it was "quite high." Two days later, because of a persistent headache that was not responsive to acetaminophen or ibuprofen, he tried chiropractic manipulation, with no improvement. He had been seen by his primary-care physician 2 days before his emergency department visit and was placed on metoprolol for hypertension, as well as gabapentin, indomethacin, and amitriptyline for what was diagnosed as a "vascular headache." Examination in the emergency department revealed normal and stable vital signs. There was anisocoria (right pupil outside diameter 3 mm; left eye 2 mm). Pupillary response to bright light was said to be normal and symmetric and the right fundus was reported to be normal. The left fundus could not be visualized. Because he had not had a history of headaches in the past, an unenhanced computed tomography (CT) scan of the brain was obtained in the emergency department and interpreted to be normal (Figure 8-1). The patient was reassured and dismissed.

Five days after his emergency department visit, he continued to suffer from headache, but traveled by air for 1 hour to a location where he was scheduled to give a lecture. Just after lying down for a brief rest, he suffered a generalized tonic clonic seizure. He was transferred to a local teaching hospital where he was intubated and mechanically ventilated and started on phenytoin. A CT scan of the brain revealed an acute right temporal lobe hemorrhage. He underwent 4-vessel angiography, which was reported to be normal. A magnetic resonance imaging (MRI) scan was obtained, which demonstrated several right temporal and parietal lobe hemorrhages (Figure 8-2). Magnetic resonance venography (MRV) demonstrated thrombosis of the right transverse sinus (Figure 8-3). A diagnosis of cerebral venous sinus thrombosis (CVST) complicated by a hemorrhagic cerebral infarction was made, no coagulation abnormality was found, and the patient was treated symptomatically. The patient continues to experience recurrent partial seizures, mild cognitive impairment, and constructional apraxia. Because of these neurologic deficits, he was forced to retire from work.

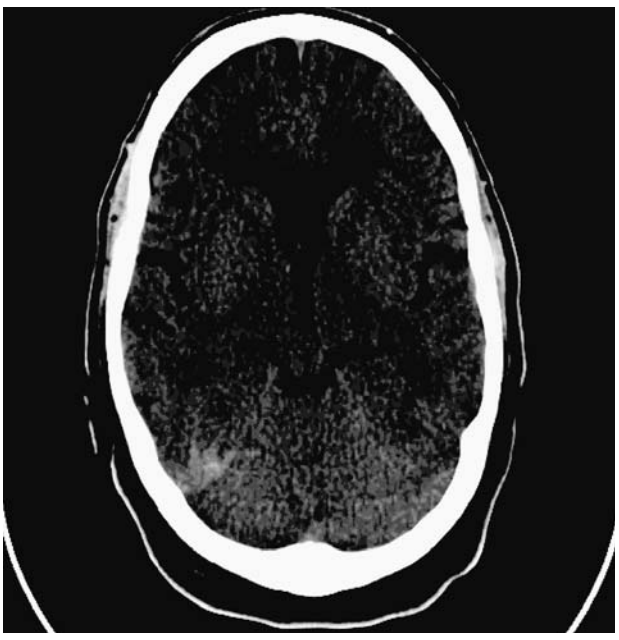

Figure 8-1. Noncontrast brain computed tomography image.

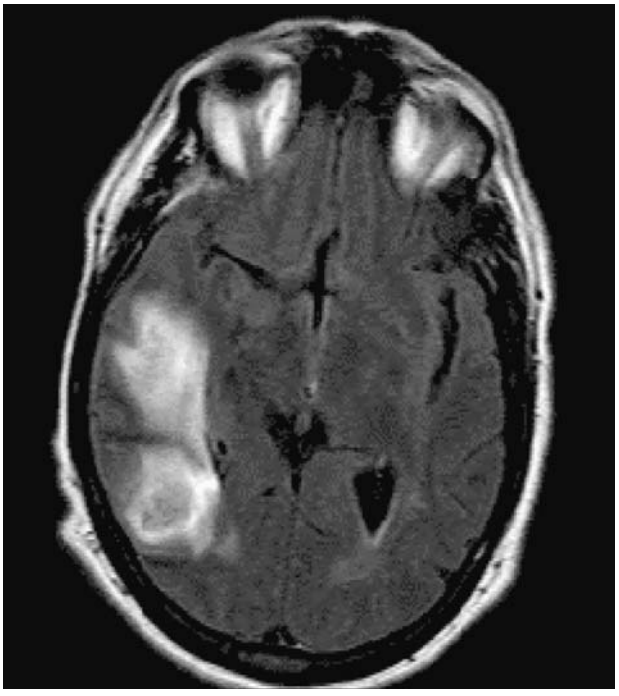

Figure 8-2. Fluid attenuated inversion recovery (FLAIR) magnetic resonance image of hemorrhagic infarction of the right temporal lobe.

Questions on the Case

Please read the questions, try to answer them, and reflect on your answers before reading the author's discussion.

- Why was the diagnosis in this case missed?
- To ensure that a potentially catastrophic cause is not overlooked, what is the single most important question for a patient who comes to the emergency department with a chief complaint of headache?
- What differential diagnosis should be formulated in patients who present with a thunderclap headache?
- If a patient with thunderclap headache has a normal CT and cerebral spinal fluid (CSF) examination, are additional studies necessary? If so, what studies should be obtained and how urgently should they be performed?

Thunderclap Headache

Thunderclap headache (TCHA) refers to an excruciating headache of instantaneous onset—as sudden and as unexpected as a "clap of thunder." In its recent revision, the International Headache Society (IHS) defined *primary* TCHA as a high-intensity headache of abrupt onset mimicking that of ruptured cerebral aneurysm. They proposed operational diagnostic criteria (Table 8-1), but admonished that the evidence to support TCHA as a primary condition is poor and that the search for an underlying cause should be expedient and exhaustive. The IHS makes clear that primary TCHA should be the diagnosis only when all organic causes have been excluded.

Differential Diagnosis of Thunderclap Headache

Although primary TCHA may represent a unique primary headache syndrome, a sudden severe headache can also occur as the presenting feature of a number of benign primary headache disorders, such as primary sexual, cough, and exertional headaches. However, TCHA may also occur as a result of a variety of sinister intracranial and extracranial vascular pathologies (Table 8-2).

Disorders Associated with Thunderclap Headache

Thunderclap headache with normal neurologic examination can be the presenting feature of disorders that may evade detection by CT and even lumbar puncture. These disorders are presented below.

Cerebral Venous Sinus Thrombosis

Headache is the most common symptom of CVST and occurs as the most frequent presenting symptom in about 75% of cases. Although a significant number of patients present with focal neurologic symptoms, seizure, or altered level of consciousness, TCHA may be the presenting feature in up to 10% of patients with CVST. In this particular case, isolated TCHA was the presenting feature. Overall,

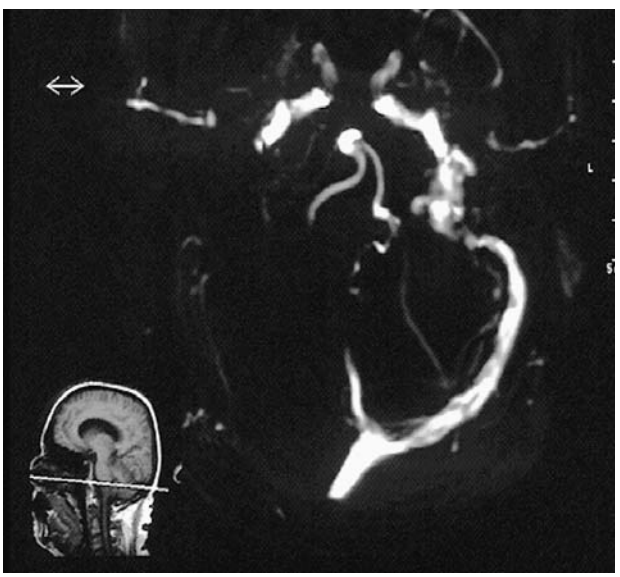

Figure 8-3. Magnetic resonance venogram showing absent flow in the right transverse and sigmoid sinuses.

Table 8-1. Diagnostic Criteria

A. Severe head pain fulfilling criteria B and C
B. Both of the following characteristics:
   1. Sudden onset, reaching maximum intensity in < 1 minute
   2. Lasting from 1 hour to 10 days
C. Does not recur regularly over subsequent weeks or months
D. Not attributed to another disorder

Notes:
1. Headache may recur within the first week after onset.
2. Normal cerebral spinal fluid and normal brain imaging are required.

CT scans are interpreted as normal in about 25% of patients with CVST. This proportion may exceed 50% in patients with CVST manifested solely by intracranial hypertension. Although some combination of lymphocytic pleocytosis, red blood cells, and elevated protein are present in 30 to 50% of published cases, up to 40% of patients with CVST may have elevated opening pressure without alteration in cytochemistry studies. For radiologic diagnosis of CVST, brain MRI and MRV should be the initial investigation. As seen in this case, the diagnosis was not only missed on the initial CT, but also on the MRI and angiography performed after the hemorrhage. This case illustrates the importance of an MRV or a venous phase of angiography when venous sinus thrombosis is suspected.

Carotid Artery Dissection

Headache is the earliest and most common symptom of internal carotid artery (ICA) dissection, occurring in up to 75% of patients. A syndrome of oculosympathetic paresis (Horner's syndrome) and unilateral headache, especially in the anterior head region (jaw, face, orbit, temporal region), is strongly suggestive of ICA dissection. Acute hemicranial headache with delayed focal cerebral ischemic events is also a common presentation of ICA dissection. The mode of onset of headache is instantaneous and severe, and in approximately 13% of cases, headache is the only symptom of ICA dissection. Unless accompanied by ischemic stroke, CT scanning and lumbar puncture are unrevealing and magnetic resonance angiography (MRA) is fast becoming the imaging modality of choice in demonstrating the arterial dissection. The outcome of ICA dissection is generally favorable, but permanent neurologic deficits and even death may result. Although no controlled trials are available, early identification of arterial dissection may allow early initiation of antiplatelet or anticoagulation therapy, possibly preventing more serious cerebral ischemic complications.

Table 8-2. Thunderclap Headaches

Secondary	Primary
Subarachnoid hemorrhage	Primary thunderclap headache
Cerebral venous sinus thrombosis	Benign cough headache
Arterial dissection	Benign exertional headache
Pituitary apoplexy	Benign sexual headache
Acute hypertensive crisis / encephalopathy	
Spontaneous intracranial hypotension	
Call-Fleming syndrome	
Unruptured vascular malformation (mainly aneurysm)	
Colloid cyst third ventricle	
Acute sinusitis (especially with barotraumas)	

Spontaneous Intracranial Hypotension

Thunderclap headache occurs in up to 15% of patients with spontaneous intracranial hypotension due to a cerebrospinal fluid leak. The clinical presentation of a sudden orthostatic headache should suggest this entity as a possibility. A low opening CSF pressure on lumbar puncture and MRI evidence of brain descent, cerebellar tonsillar herniation (secondary Chiari malformation), pachymeningeal thickening and enhancement, and subdural hematomas can support this diagnosis. Spinal MRI may detect extra-arachnoid fluid collections and may locate the region of the leak, which is often in the lower cervical or upper thoracic spine. Radionuclide cisternography may support the diagnosis of a CSF leak (early collection of radionuclide in the urinary bladder and failure of the radionuclide to collect over the cerebral convexities by 24 hours). Cisternography may also demonstrate the site of the leak. However, CT with myelography remains the most sensitive method to localize the site of a spinal CSF leak.

Pituitary Apoplexy

Pituitary apoplexy can present with TCHA in the absence of positive findings on clinical, CT, or CSF examinations. Pituitary apoplexy is an uncommon clinical syndrome, usually characterized by acute headache, ophthalmoplegia, diminished visual acuity, and altered mental status. It is caused by the sudden infarction or hemorrhage of a pituitary gland that invariably harbors an adenoma. The clinical manifestations of pituitary apoplexy, however, are protean, ranging from a clinically benign event to a catastrophic illness with adrenal crisis, coma, or sudden death. Pituitary tumors, isodense to brain tissue, can easily be overlooked on routine CT, even when hemorrhage is present within the gland. An MRI readily identifies both the tumor and the associated hemorrhage.

Unruptured Intracranial Aneurysms

The prevalence of intracranial aneurysms is between 3 to 6% in the general population and, therefore, the possibility of detecting an incidental aneurysm in a patient with primary TCHA is not remote. Whether or not unruptured intracranial aneurysms can present with TCHA is thus still a matter of debate. The pressing question of course is

whether any or all patients with TCHA, in whom the initial CT and lumbar puncture is negative, should undergo conventional angiography.

In 1986, the term "thunderclap headache" was introduced to describe a similar headache as a presenting feature of an unruptured cerebral aneurysm. The authors reported a 42-year-old woman who suffered three TCHAs within 1 week. The CT brain and CSF examinations were normal. Despite the absence of blood within the CSF, conventional angiography revealed diffuse, multifocal, and segmental cerebral vasospasm and a saccular aneurysm at the point of origin of the right posterior cerebral artery. Even so, no evidence of old or recent hemorrhage was seen during aneurysmal surgery. Four weeks later, the follow-up angiogram was normal. The authors concluded that unruptured intracranial aneurysms can present with TCHA and that cerebral angiography is necessary in these patients even when the CT and CSF examinations are normal. In addition to several similar cases, two retrospective series have been reported.

In one retrospective series, 7 of 111 patients with symptomatic unruptured saccular aneurysms were said to have presented with TCHA. Unfortunately, not all patients in this study had CSF examinations, and there were abnormal neurologic findings or other clinical and imaging features that pointed to an underlying cause for the headache. This study, therefore, did not address patients with TCHA who have normal CT, CSF, and neurologic examinations. In another retrospective series, 562 patients presented with sudden severe headache, normal CT, and "colorless" CSF. Cerebral aneurysms were found in 52 patients (9.3%). Of the 46 patients who were taken to surgery, 8 (1.4%) had a "minor leak," although it is unclear exactly how this was determined. Collectively, these data have prompted the recommendation that because of the potentially devastating consequences of overlooking a symptomatic saccular aneurysm, angiography should be obtained in patients with TCHA and a normal CT, CSF, and neurologic examination.

The balance of evidence suggests that for most patients with TCHA with normal initial CT scans and lumbar puncture, subarachnoid hemorrhage does not occur. In a retrospective study of 71 patients with TCHA and normal CT and lumbar puncture results, none of the patients had subarachnoid hemorrhage during an average follow-up period of 3.3 years. Moreover, in four prospective studies, a total of 225 patients with TCHA and negative CT and lumbar punctures were followed for 1 year or more, and none of the patients had a subarachnoid hemorrhage or sudden death.

Therefore, the overwhelming majority of patients who present with TCHA and have normal CT and CSF examinations will not harbor a *symptomatic* cerebral aneurysm, and in the absence of other intracranial causes, the outcome and prognosis appear to be benign. The issues as to which patients require further investigation and which diagnostic studies are required depend upon the clinical index of suspicion and the comfort level of both the patient and clinician.

Acute Hypertensive Crisis

Headache occurs in approximately 20% of patients during a hypertensive emergency, and although the headache is usually throbbing and nondistinct, TCHA has been reported in association with hypertensive encephalopathy and posterior leukoencephalopathy syndrome (PLES). PLES is a rapidly evolving neurologic condition characterized by headache, nausea and vomiting, visual disturbances, altered mental status, decreased alertness, seizures, and occasionally, focal neurologic signs. PLES is associated with an abrupt and severe increase in blood pressure in most cases, including patients with eclampsia or renal disease with hypertension. The main finding in neuroimaging and autopsy studies is posterior white matter edema, particularly involving the parietal and occipital lobes, which may spread to the basal ganglia, brainstem, and cerebellum.

Complete clinical and radiologic recovery often occurs with prompt antihypertensive treatment or withdrawal of the immunosuppressive drug. Occasionally, the clinical features and CT or standard MRI findings may be difficult to distinguish from a bilateral posterior cerebral artery stroke syndrome. Thus, early recognition of PLES is essential.

Multifocal and segmental cerebral vasospasm can also been seen in association with a hypertensive crisis. The mechanism of vasospasm in primary TCHA and in patients with hypertensive crises may be related to a loss of autoregulation, resulting in dilatation of cerebral arterioles and disruption of the blood-brain barrier.

Call-Fleming Syndrome

In 1988, Call and colleagues reported 4 patients and reviewed a total of 19 patients from the literature who presented with a self-limited syndrome of recurrent, sudden, high-intensity headaches ("thunderclap headache") associated with nausea, vomiting, photophobia, generalized seizures (7 of 19), recurrent transient neurologic symptoms (7 of 19), or permanent neurologic deficits such as hemiparesis and cortical blindness (4 of 19). Three patients became comatose and died. The common finding in all patients was the presence of diffuse segmental cerebral vasospasm involving the distal internal carotid, basilar, and major arteries of the circle of Willis, which was fully reversible within weeks to months. Brain and/or cerebral blood vessel biopsies were negative in 6 of 19 patients, and CSF examinations were mildly abnormal in 5 patients (3 patients with elevated CSF protein [51 to 125 mg/dL]; 2 patients with CSF lymphocytic pleocytosis

[6 to 16 white blood cells]). They felt that the segmental vasospasm was likely due to a physiologic abnormality, given the lack of a structural correlate, cellular infiltrate, or hypertension in most patients.

As the literature continues to grow with case reports of this unusual disorder, the clinical spectrum is becoming more refined. As these and other cases illustrate, the clinical–angiographic syndrome of recurrent TCHAs, diffuse reversible vasospasm, and delayed ischemic deficits may occur spontaneously or secondary to an underlying metabolic, hemodynamic, or biochemical (endogenous or exogenous) insult. The headaches are often occipital/posterior, and although the arteriographic evidence of vasospasm is diffuse, multisegmental, and can involve the anterior and posterior circulation, the delayed ischemic insults often occur in either an arterial borderzone or in a parietal–occipital distribution.

Several reports have raised the possibility that calcium channel antagonists may reverse vasospasm and potentially limit or prevent the development and/or severity of the delayed neurologic deficits. The rationale for using calcium antagonists in patients with vasospasm related to subarachnoid hemorrhage is based on the notion that these drugs counteract the influx of calcium in the vascular smooth-muscle cell, a mechanism which is central to the regulation of smooth-muscle contractility. Because it is unlikely there will ever be a randomized trial of calcium antagonists in this syndrome, the recommendation to administer nimodipine to patients with Call-Fleming syndrome who develop neurologic symptoms or signs in the presence of diffuse vasospasm, appears to be sound medical advice. The question that begs more discussion is whether all patients with unprovoked TCHA and diffuse cerebral vasospasm should receive prophylactic nimodipine, particularly in light of the fact that hypotension, which occurs in up to 15% of patients treated with nimodipine, could further compromise cerebral blood flow in these patients. However, even though not all patients develop neurologic symptoms or signs, given the severe neurologic sequelae that have occurred in some patients, a brief course of nimodipine may be prudent. Obviously, careful clinical observation over the initial 2 to 3 weeks is crucial, as most deficits appear to be delayed by 1 to 3 weeks.

Case Discussion

A secondary cause for TCHA was missed in this patient's case because an adequate history was not obtained, a differential diagnosis was not generated, and appropriate investigations were therefore not pursued. Every patient presenting with headache as a chief complaint must be interrogated for clinical features that should raise the suspicion of a secondary cause for headache (Table 8-3). This is particularly true in patients presenting to the emergency department, where the prevalence of secondary causes for headaches is higher than in ambulatory care. Perhaps the two most important issues in these patients are the onset of the headache and previous headache history. Patients do not always volunteer this information and it is the physician's task to elicit these features by direct questioning. In this particular patient, he had a TCHA that began abruptly and with peak intensity from onset. In addition, he had no history of having experienced headaches of any type in the past. Furthermore, the appropriate investigation after an initially normal CT and lumbar puncture would have been an MRI with MRV and MRA to exclude other etiologies, such as arterial dissection and venous sinus thrombosis, which may be missed on these initial investigations.

Table 8-3. Secondary Headaches: Worrisome Clinical Features

Systemic symptoms (myalgia, fever, malaise, weight loss, jaw claudication, etc) or
Systemic disease (eg, cancer, HIV infection)
Neurologic symptoms (focal) or abnormal exam findings (confusion, seizures, impairment in level of consciousness or alertness, etc)
Onset: sudden, abrupt, split-second, or thunderclap
Older: new onset or progressive headache, especially in middle age (> 50 years) or later, or a significant change in a long-standing headache
Previous headache history: first or worst, or different (change in attack frequency, severity, or clinical features)

Overview of the Case

Since patients with subarachnoid hemorrhage can present with TCHA in isolation, all patients require an unenhanced CT scan of the brain, and if negative, a lumbar puncture to assess for subarachnoid blood and xanthochromia. In the absence of blood on both the CT and lumbar puncture, further investigations are *mandatory* to exclude the other potentially devastating yet treatable disorders which are outlined above. If available, an MRI with an MRA and MRV should be obtained. If not, the patient should be transferred to a facility with this technology. Alternatively, angiography couldbe performed, but as illustrated in this case, unless a delayed venous phase is obtained, cerebral venous sinus or cortical vein thrombosis can easily be overlooked.

Selected Readings

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Editorial Comments

Few headache disorders strike such fear in the heart of neurologic diagnosticians as TCHA. Such a presentation immediately evokes a sense of urgency and a need to act quickly to exclude a sinister diagnosis such as an aneurysm causing a subarachnoid bleed. However, there is more to the story of TCHA than most doctors recognize, and Dr. Dodick's chapter and work in this area has been most helpful in defining the limits of this particular headache disorder. TCHA can be benign in nature, but that is something that can only be considered in retrospect at such time that serious etiologies are excluded, including cerebral vein thrombosis, a frequently more recognized etiology. This chapter puts TCHA in perspective and, as such, helps in daily practice.

Final diagnosis:

Secondary thunderclap headache