Chapter 54

The Innocuous Headache that Turned Sinister

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Case History

A 42-year-old businessman was seen in our Headache Clinic with complaints of near-daily, continuous head pain for 2 weeks prior. This was the first time in his life that he had experienced such a headache. The pain was restricted to the right hemicranium, was mildly throbbing in nature, and then gradually progressed to a generalized headache that was unbearable. There were no specific relieving factors, and analgesics only afforded mild relief.

There was no history of vomiting, photophobia, phonophobia, fever, or other neurologic or systemic accompaniments. There was no history of head or neck trauma and there were no indicators to suggest an extracranial infection or systemic illness that would explain this new-onset headache in an otherwise healthy individual. There were no triggers or aggravating factors and no postural worsening. He was not hypertensive or diabetic, and there was no past history of migrainous headaches in him or his family members.

His general physical and neurologic examinations were normal, with a blood pressure of 130/90 mm Hg, and temperature was normal. Pupillary examination and fundoscopy were normal, there was no papilledema; the cranial nerves and the remainder of the neurologic examination were normal.

In view of the new onset of headache, and the clinical examination being noncontributory, he was advised to have a computed tomography (CT) head scan on an outpatient basis, following which further specific management and further investigations were to be planned as necessary. In the meantime, he was prescribed stronger analgesics.

He had the CT scan done over the weekend and telephoned the clinic to say that his scan was reported normal, but the very next day (ie, 3 days after his outpatient consultation), he was rushed to the intensive-care unit (ICU) in an unconscious condition with a series of generalized convulsions and mild right hemiparesis.

Questions on the Case

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

- Given this gradual onset and progressive worsening with convulsions and hemiparesis, what would your provisional working diagnosis be? What other conditions would you like to consider in the differential diagnosis?
- What further testing would you ask for? Was there any way this catastrophe could have been preempted?
- What would be the ideal investigation in a patient who presents with a new onset, progressively worsening headache?
- How would you further investigate and treat this patient? What is the prognosis?

Progress

On examination in the ICU, the patient was unconscious and poorly responsive to painful stimuli. The temperature was normal, blood pressure was 130/90 mm Hg, there was no neck stiffness, pupils were equal but sluggish in reaction, and there was early papilledema that was not seen earlier. He had mild right hemiparesis and both plantars were extensor. Systemic examination was normal.

The convulsions were brought under control with parenteral phenytoin and diazepam. He was started on antiedema measures and antibiotics. His CT scan that was

done 2 days prior to admission was normal and was nonrevealing, even when reviewed keeping in mind this new development. A magnetic resonance imaging (MRI) scan was ordered, which showed thrombosis of the left sigmoid and transverse sinus with a fairly large temporoparietal acute hematoma and multiple fluid levels within it, suggestive of a hemorrhagic venous infarct with areas of recurring bleed. There was significant adjacent mass effect with perilesional edema causing a subfalcine herniation. There was evidence of bleed within the right lateral ventricle.

With a confirmed diagnosis of cerebral venous thrombosis (CVT), he was investigated extensively, keeping in mind the various underlying causes that could contribute to venous occlusion. Even after detailed investigations, there was no underlying cause that could be identified. He was anticoagulated routinely, first with intravenous heparin and then with low molecular weight heparin. His level of consciousness improved, but he was left with dysphasia and residual right hemiparesis. After a prolonged hospital stay, he was discharged home on oral anticoagulants.

Case Discussion

This patient had thrombosis of the left sigmoid and transverse sinus that progressed to a hemorrhagic venous infarct. The innocuous presentation in an office setting, with headache alone and normal clinical examination, and the rapid worsening to the point of admission to the ICU in a comatose state, are indicative of the complex diagnostic and therapeutic challenge of CVT.

There are several lessons to be learnt from this patient's case. With modern neuroimaging techniques, CVT is being diagnosed much more frequently and is not

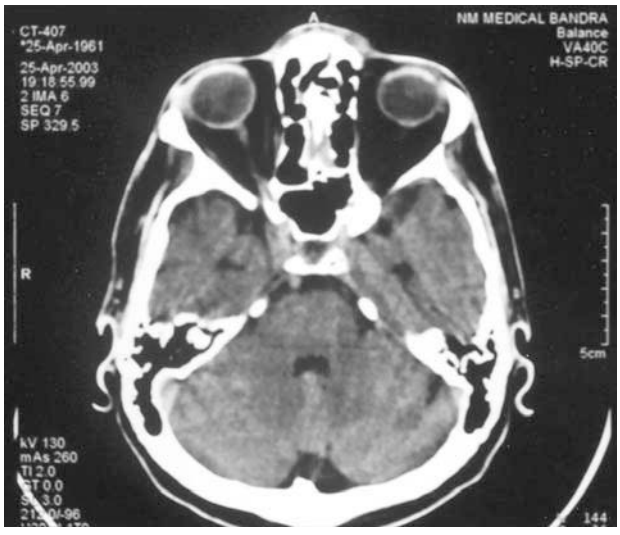

Figure 54-1. Contrast-enhanced axial computed tomography brain image revealing normal contrast opacified sigmoid sinuses.

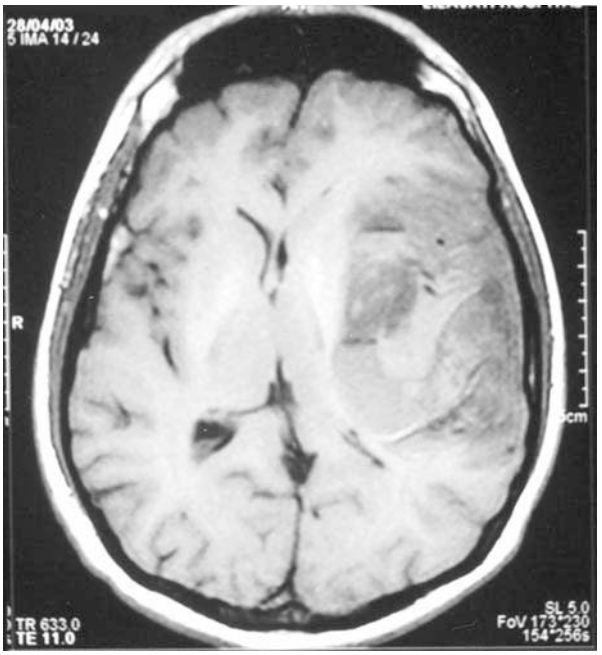

Figure 54-2. T1-weighted axial magnetic resonance image of the brain showing a heterogeneously hypointense lesion in the left temporoparietal region, with mass effect on ipsilateral ventricle and minimal subfalcine shift to the right.

so uncommon as generally portrayed. Although it is a well-recognized fact that CVT can mimic any brain disorder, and can present acutely with a vast array of clinical presentations that include headache, seizures, focal deficits, intracranial hypertension, and papilledema, it is not so well known that CVT can also present subacutely and even progress slowly. Headache is known to be the most frequently associated initial complaint, and is present in more than 80% of patients, but *it is not always remembered that headache can be the sole presenting complaint of CVT*. When there is a typical picture or a background setting, the diagnosis is not difficult, but when the patient walks into the outpatient clinic with just head pain that has no specific clinical characteristics or temporal profile, and there are no additional indicators of the diagnosis and there is no typical setting that can predispose to venous occlusion, then it becomes almost impossible to arrive at the diagnosis of CVT. This delay can sometimes lead to catastrophic consequences—so there is a need for a high index of suspicion!

Given the fact that headache can occur in isolation, that it can present with a varying mode of onset, that it can be unilateral, that it can be localized to any region of the head, that it can vary in "severity," and that it can be intermittent initially and become constant later, one must keep in mind the possibility of CVT in every patient who presents with new-onset headache of any type, any sever-

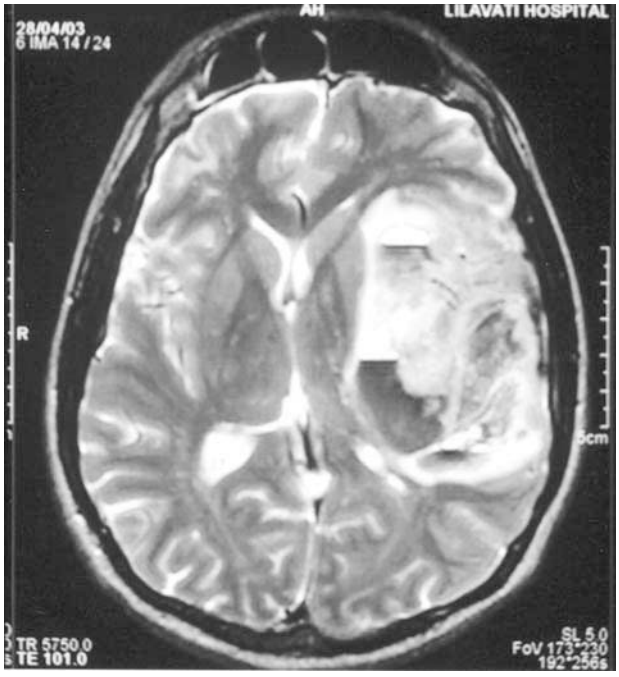

Figure 54-3. T2-weighted axial magnetic resonance image of the brain at the same level as Figure 54-2, showing the left temporoparietal lesion to be heterogeneous, with few areas of hypointensity and a fluid–fluid load signifying bleed within the lesion.

ity, and in any location, particularly when there is worsening in spite of analgesics.

When the headache of CVT is accompanied by focal deficits, seizures, drowsiness, or papilledema, the patient generally presents to the emergency department and is investigated more aggressively. An MRI, MR angiography, MR venography (MRV), and other testing may be ordered in order to establish the diagnosis, as well as to rule out other conditions such as an ischemic or hemorrhagic stroke, abscess, tumor, and encephalitis that could present with similar features. But when CVT presents with headache alone, in isolation, without accompanying papilledema or other signs and symptoms, and when the patient consults in an office setting, then investigations may stop short with a CT scan that often turns out to be normal. We often get misled because we have been led to believe that CVT is usually an emergency department diagnosis, acute in onset, and that it always needs a setting. *So an MRI scan with MRV is not requested because there is no suspicion of CVT*.

Furthermore, ordering a CT scan as the first test has certain drawbacks. The CT scan may be normal in up to 30% of patients with CVT, and is of use mainly to rule out other brain syndromes that CVT can mimic such as subarachnoid bleed, ischemic or hemorrhagic stroke, abscess, or tumor. A plain CT can sometimes detect the spontaneously hyperdense thrombosed sinus, and the empty triangle (or delta sign) of superior sagittal sinus thrombosis may be seen after contrast, but it usually shows only nonspecific changes (Table 54-1).

Whenever CVT is suspected in a patient with a new-onset headache, an ideal test that is nowadays perhaps regarded as the gold standard for diagnosis of CVT would be an MRI with MRV, where the thrombosed sinus can be visualized by increasing signal on T1- and T2-weighted imaging. It is the only study that visualizes the thrombosis itself as an increased signal on T1- and T2-weighted imaging, and is most obvious between day 5 and day 30. MRV, helical CT venography, or conventional angiography are indicated for very early or late stages. MRI can show the consequences of thrombosis such as cerebral edema, infarction, and hemorrhage, as well as the anatomy of the disturbed venous circulation. More recently, CT venography has been shown in one series to be superior to MRV in visualizing sinuses or smaller cerebral veins or cortical veins with low flow.

CVT was first described by Ribes in 1825, and was for a long time considered to be always fatal and diagnosed only at autopsy. There are several typical presentations of CVT. Eighteen to 38% present with a syndrome resembling benign intracranial hypertension with headache, papilledema, and visual disturbances. This stresses the importance of doing an MRI and/or angiography in all patients who present with "pseudotumor cerebri." When thrombosis involves the dural sinuses and dural veins, the presentation may be with headache, focal signs, and progression to seizures or loss of consciousness. CVT presenting as thunderclap headache with neck stiffness mimicking subarachnoid hemorrhage has also been described. Cavernous sinus thrombosis presents with chemosis, proptosis, and painful ophthalmoplegia that may be unilateral or bilateral. All patients with CVT may progress in their clinical presentation. Worsening can occur due to extension of the thrombus to the cortical veins.

Once CVT is diagnosed, the next step is to investigate further to try and establish the etiology. Predisposing factors can be identified in up to 80% of cases. This includes

Table 54-1. Other Conditions with Headache and Normal Computed Tomography Scans

Carotid or vertebral dissection
Central nervous system vasculitis
Isodense subdural hematomas
Encephalitis
Meningitis
Infiltrative gliomas
Pituitary tumor
Spontaneous intracranial hypotension
Benign intracranial hypotension

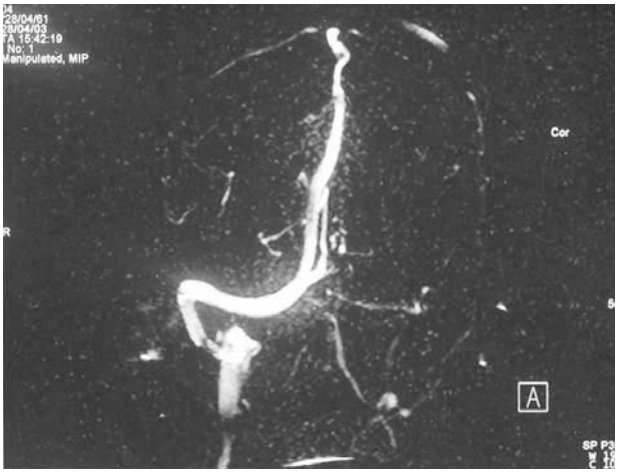

Figure 54-4. Magnetic resonance venogram showing nonvisualization of the left transverse sinus and internal jugular vein and paucity of cortical veins.

all conditions that can predispose to deep vein thrombosis. Puerperium and, to a lesser extent, pregnancy are the most commonly identified causative factors. Here, the onset is most commonly acute and from 1 to 20 days after delivery or during the second or third trimester of pregnancy. CVT can occur at any age. Infective causes have decreased with earlier antibiotic usage, but otitis media, meningitis, and sinusitis still need to be kept in mind. Amongst the noninfective causes, systemic conditions such as connective tissue diseases, granulomatous and inflammatory disorders, Behcet's disease, and underlying malignancies are common. Hereditary prothrombotic hypercoagulable disorders such as activated protein C resistance (factor V Leiden), particularly in combination with oral contraceptives, deficiency of proteins C and S and antithrombin III, as well as prothrombin gene mutations may account for 10 to 15% of CVT (Table 54-2).

Cerebral spinal fluid (CSF) examination is important to rule out other conditions and to confirm raised CSF pressure and benign intracranial hypertension. In 20 to 30% of cases, in spite of extensive search, no underlying cause may be found, and these patients need close follow-up and repeat investigations (Table 54-3), if need be, to establish the etiology. Coagulation studies need to be performed twice; once before starting anticoagulation and once after completion of treatment.

The main cerebral venous sinuses affected by CVT are the superior sagittal sinus (72%) and the lateral sinus (70%). In one-third of cases, more than one sinus may be affected; in a further 30 to 40%, both sinuses and cerebral or cerebellar veins are involved. Although sudden in onset, gradual progression of the venous thrombosis is the rule, and the good collateral circulation probably explains the gradual onset over weeks or months. Hemorrhagic infarction occurs in 10 to 50% cases.

Table 54-2. Causes and Predisposing Factors of Cerebral Venous Thrombosis

Infective
Intracranial infection
Penetrating head injury
Regional infection
Sepsis and systemic infection
Noninfective
Hematologic
Hyperviscosity
Primary/secondary thrombocytopenia
Paroxysmal nocturnal hemoglobinuria
Polycythemia
Gynecologic/Obstetric
Pregnancy and puerperium
Oral contraceptives
Coagulation Disorders
Antithrombin III deficiency
Activated protein C resistance
Factor V Leiden mutation
Protein C or S deficiency
Disseminated intravascular coagulation
Anticardiolipin antibody syndrome
Vasculitis
Behcet's disease
Wegener's granulomatosis
Sarcoidosis
Giant cell arteritis
Systemic lupus erythematosus
Malignancies
General
Severe dehydration
Postsurgical
Cardiac failure
Nephrotic syndrome

Management Strategies

Treatment should be started at the earliest possible time. You may consider treating the cerebral edema with antiedema measures, the seizures with anticonvulsants, and the underlying cause specifically. Anticoagulants are necessary to prevent extension of the thrombus.

Table 54-3. Laboratory Investigations to be Done in Suspected Cerebral Venous Thrombosis

Complete blood count, erythrocyte sedimentation rate
Triiodothyronine (T_3), thyroxine (T_4), thyroid-stimulating hormone
Electrocardiogram, two-dimensional echocardiography
Rheumatoid arthritis, anti-dsDNA
Serum creatinine
Tests to rule out malignancy
Coagulation profile for prothrombotic disorders

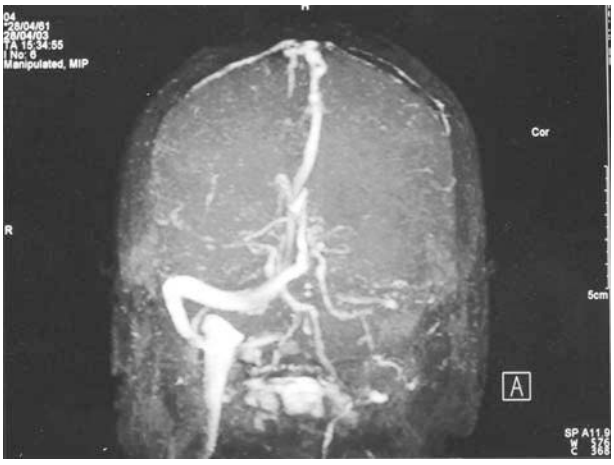

Figure 54-5. Magnetic resonance venogram revealing nonvisualization of the left transverse sinus and left internal jugular vein with paucity of cortical veins.

Intravenous heparin may be used, with all necessary precautions, as the favored drug of choice, even when there is a hemorrhagic infarct. Routine intravenous heparin may be replaced by low molecular weight heparin. As soon as improvement starts, oral anticoagulation with warfarin should be started. If, even after heparin, there is deterioration due to thrombus extension, then local thrombolysis or recombinant tissue-type plasminogen activator (rtPA) can be tried. Complete recanalization is more frequent and faster with rtPA plus heparin than with heparin alone. Oral anticoagulation is recommended for 3 to 6 months following the acute phase, except when there is a known prothrombotic condition, in which case treatment may have to be life long.

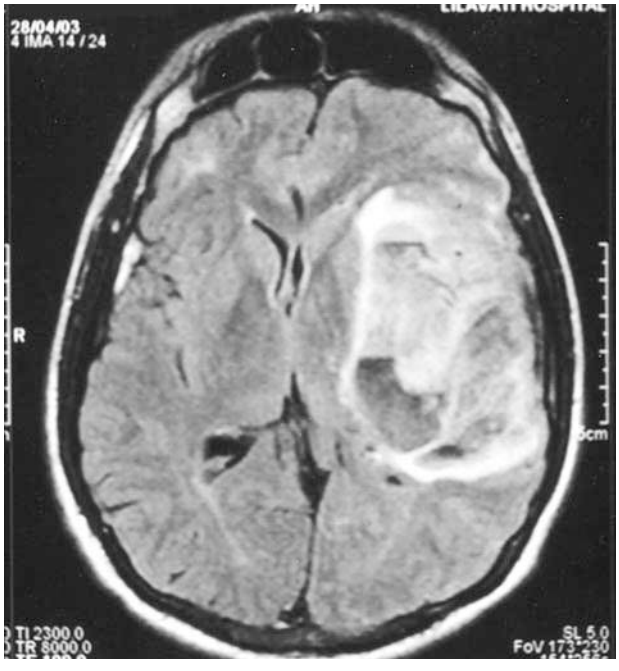

Figure 54-6. Fluid attenuated inversion recovery (FLAIR) axial magnetic resonance image of the brain showing the left temporoparietal lesion to be heterogeneously hyperintense.

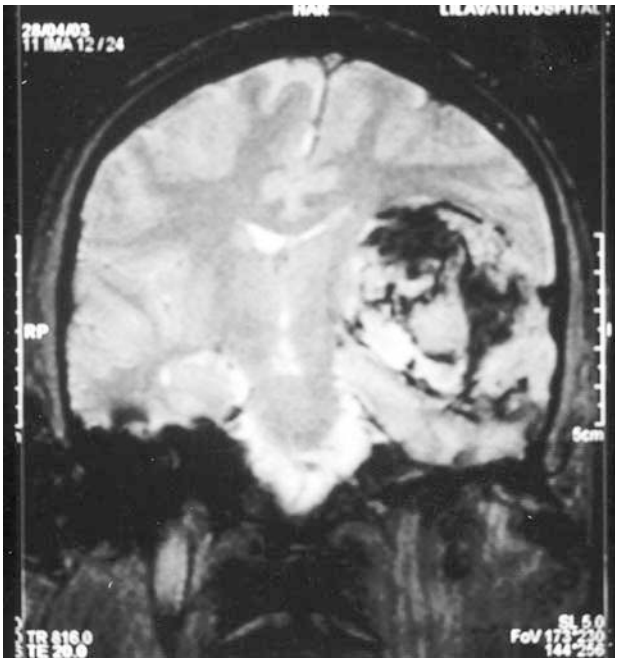

Figure 54-7. Fast low-angle shot (FLASH) two-dimensional coronal image of the brain showing blooming of the hypointensity within the lesion, suggestive of deoxyhemoglobin.

The prognosis for CVT is more favorable than generally thought, but remains unpredictable. There is no clear correlation between disease severity and outcome, but several factors are associated with poor prognosis: infancy, advanced age, rapid onset with coma, and thrombosis affecting largely the deep venous system. Sepsis, malignancy, and paroxysmal nocturnal hemoglobinuria also adversely affect outcome. The two main prognostic factors are the location of the thrombus and the underlying cause. Deep cerebral and cerebellar vein thrombosis and septic causes have a high mortality.

Conclusion

In the past and even today, CVT is considered uncommon, and is thought of as a neurologic emergency that is characterized by seizures, papilledema, focal deficits, and coma. With the onset of advanced neuroimaging, particularly MRI and MRV, the scenario is now changing. CVT is more common than was thought, it can present with headache alone, it does not always present with a background setting, it is best diagnosed by MRI,

and it can progress rapidly if not treated early. With timely treatment using heparin, the outcome can be favorably altered. It is truly a clinical diagnosis that most neurologists, who miss it the first time, remember for a lifetime!

Summary

- In the past, a CVT was thought to be uncommon. It is diagnosed more commonly now because of advances in neuroimaging.
- CVT should be considered in any brain syndrome with headache and even when there is just headache alone. Headache can occur in isolation in up to 5% of cases.
- CVT can present suddenly, subacutely, or progress slowly with headache of any type, location, or severity. The most common clinical presentation is with benign intracranial hypertension and papilledema.
- CT as the first diagnostic test may miss a number of cases. CVT is best picked up by MRI and confirmed by MRV.
- CVT does not necessarily occur only when there is an obvious underlying etiology. In almost 30% of cases, the etiology cannot be established.
- When no cause is found, it is advisable to follow up on a long-term basis.
- Noninfective causes are more commonly seen nowadays than infective causes. Systemic disorders, connective tissue diseases, and malignancy need ruling out.
- CVT can present at all ages, but is seen more in young and middle-aged women.
- Heparin must be used for treatment in all. Risky therapeutic strategies must be used only when there is poor prognosis.
- If diagnosed early and treated early, the prognosis and outcome are favorable, as there is extensive collateral circulation in the cerebral venous system.

Selected Readings

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Editorial Comments

Cerebral vein thrombosis is a potentially lethal diagnosis and must not be missed. This case outlines, with great clarity and detail, the approach and management of such a case. For headache doctors, the problem is rather problematic. Any headache presentation can occur in CVT. When the presentation is one of thunderclap headache in the emergency room, then usually, but not always, the diagnosis is made, even if not initially considered. However, as pointed out by Dr. Ravishankar, the setting remains very important, as lesser degrees of headache may be mistaken for primary headache disorders, and a negative CT does not rule out CVT and many other serious causes of headache, for that matter. The remarkable advent of MRI, and in particular the use of MRV, and new modalities, have made this diagnosis a lot more common. If you see a lot of headache patients, always consider CVT to be a cause of secondary headache, especially in a new or sudden headache. If given the scrutiny of another potentially lethal disorder that is subarachnoid bleed, then less will be missed in the future. CVT is treatable and can be diagnosed—one has to just "think about it," and as Dr. Ravishankar says, once you diagnose one case, you will never forget it.

Final diagnosis:

Cerebral vein thrombosis