Thunderclap headache

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Thunderclap headache (TCH) is head pain that begins suddenly and is severe at onset. TCH might be the first sign of subarachnoid haemorrhage, unruptured intracranial aneurysm, cerebral venous sinus thrombosis, cervical artery dissection, acute hypertensive crisis, spontaneous intracranial hypotension, ischaemic stroke, retroclival haematoma, pituitary apoplexy, third ventricle colloid cyst, and intracranial infection. Primary thunderclap headache is diagnosed when no underlying cause is discovered. Patients with TCH who have evidence of reversible, segmental, cerebral vasoconstriction of circle of Willis arteries and normal or near-normal results on cerebrospinal fluid assessment are thought to have reversible cerebral vasoconstriction syndrome. Herein, we discuss the differential diagnosis of TCH, diagnostic criteria for the primary disorder, and proper assessment of patients. We also offer pathophysiological considerations for primary TCH.

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Introduction

Thunderclap headache (TCH) is an acute and severe headache that is maximum in intensity at onset and has been likened to a "clap of thunder". The term TCH was initially used by Day and Raskin[1] in reference to the pain associated with an unruptured intracranial aneurysm. However, multiple causes have since been described (panel 1). Primary TCH is diagnosed when all other potential underlying causes have been eliminated by diagnostic testing. Primary TCHs can recur intermittently and are generally associated with a benign outcome. A subset of patients with TCH has reversible and segmental vasoconstriction involving arteries of the circle of Willis. Patients presenting with TCH, reversible segmental constriction of intracranial arteries, and normal or near normal cerebrospinal fluid are diagnosed with reversible cerebral vasoconstriction syndrome (RCVS). This type of angiopathy is a unifying term for TCH with vasospasm, benign angiopathy of the CNS, migrainous vasospasm, Call-Fleming syndrome, and drug-induced cerebral vasospasm. In this review we discuss each of the underlying disorders that must be considered in the differential diagnosis of TCH, summarise the characteristics and diagnostic criteria for primary TCH and RCVS, discuss the underlying pathophysiology of TCH, and detail the diagnostic assessment of patients presenting with TCH.

***Panel 1:* Causes of TCH**

Subarachnoid haemorrhage
Sentinel headache
Cerebral venous sinus thrombosis
Cervical artery dissection
Spontaneous intracranial hypotension
Pituitary apoplexy
Retroclival haematoma
Ischaemic stroke
Acute hypertensive crisis
Reversible cerebral vasoconstriction syndrome
Third ventricle colloid cyst
Intracranial infection
Primary thunderclap headache
Primary cough, sexual, and exertional headache

Subarachnoid haemorrhage

Subarachnoid haemorrhage is the most common cause of secondary TCH and should be the focus of the initial assessment given the significant associated morbidity and mortality. Initial misdiagnosis and subsequent rebleeding corresponds with a worsening prognosis. 11–25% of patients presenting with TCH may have subarachnoid haemorrahage.[2,3] A prospective, hospital-based study of sudden onset headache by Landtblom and colleagues[2] showed that 11% of patients had subarachnoid haemorrhage. Linn and colleagues,[3] in a community-based prospective study of 148 patients with TCH reported that 37 (25%) had subarachnoid haemorrhage.

Subarachnoid haemorrhage is most commonly due to rupture of an intracranial aneurysm.[4] Ruptured aneurysms account for 85% of cases, non-aneurysmal perimesencephalic haemorrhage (with excellent prognosis) account for 10%, and various rare disorders (transmural arterial dissection, cerebral arteriovenous malformation, dural arteriovenous fistula, mycotic aneurysm, and cocaine abuse) account for the rest.[4]

Headache, which may occur in isolation or in association with other signs and symptoms, is the most common symptom in subarachnoid haemorrhage. In a community-based, prospective study,[3] 70% of patients with subarachnoid haemorrhage presented with headache alone, without loss of consciousness or focal symptoms. By contrast, in a hospital-based study, less than 50% of patients presented with isolated headache.[5] Headaches can be at maximum intensity at onset or develop rapidly, reaching their maximum within a few minutes.[6] Typically, a subarachnoid haemorrhage headache lasts a few days; it is atypical for the headache to resolve in less than 2 h.[7] Although physical exertion or sexual intercourse may precede subarachnoid haemorrhage, it can occur without physical stress and such stressors are also commonly associated with benign attacks of acute severe headache.[2,8]

Loss of consciousness occurs in a third of patients with subarachnoid haemorrhage.[3,9] Other associated

symptoms include seizures (6–9%), delirium (16%), stroke (caused by intracerebral haematoma), visual disturbances (due to intraocular haemorrhage), nausea, vomiting, dizziness, neck stiffness, and photophobia.[10–12]

Physical examination is usually of little help during assessment of patients with suspected subarachnoid haemorrhage.[13] Fundal haemorrhages occur in 20–40% of patients, more commonly in those with low levels of consciousness. Although the presence of fundal haemorrhages is helpful in diagnosing subarachnoid haemorrhage, photophobia and patient distress can make detection technically difficult.[14,15]

Non-contrast CT of the brain is the first diagnostic test in the assessment of suspected subarachnoid haemorrhage. Due to decreasing sensitivity for the detection of subarachnoid haemorrhage over time, CT should be done as soon as possible after the onset of symptoms. CT has a sensitivity that nears 100% within the first 12 h of subarachnoid haemorrhage but then falls to about 50% within 1 week.[16–20] When there is clinical suspicion of subarachnoid haemorrhage but CT results are unrevealing, lumbar puncture must be done. In addition to routine cerebrospinal fluid assessment, including cell counts and visual inspection for xanthochromia, analysis by spectrophotometry should also be done if available. In contrast to the declining accuracy of CT over time, spectrophotometry is more sensitive after the first 12 h of haemorrhage. When cerebrospinal fluid is collected at least 12 h after subarachnoid haemorrhage, spectrophotometry has sensitivity greater than 95%.[21] Patients with subarachnoid haemorrhage should undergo conventional angiography in search of a ruptured aneurysm.

Despite recent advances in the treatment of patients with subarachnoid haemorrhage, overall outcome is poor.[22,23] About 10% of patients die before reaching a hospital, case fatality is about 50% overall, and a third of survivors remain dependent.[3,24]

Sentinel headaches and warning leaks

Sentinel headaches are clinically similar to headaches that occur with subarachnoid haemorrhage; they develop rapidly, reach maximum intensity within minutes, and can last for hours to days. However, unlike subarachnoid haemorrhage, patients with sentinel headaches generally do not have meningismus, altered consciousness, or focal neurological symptoms and signs. Sentinel headaches are most probably due to a leak of blood into the subarachnoid space. However, these result in a relatively benign clinical presentation and are commonly misdiagnosed. 10–43% of patients with aneurysmal subarachnoid haemorrhage have a history of a sentinel headache or a warning leak days to weeks before aneurysm rupture.[25]

When sentinel headaches and warning leaks are recognised, appropriate diagnostic imaging should lead to detection of the underlying aneurysm. Surgical or endovascular intervention could avoid a potentially catastrophic haemorrhage. However, most patients with sentinel headaches or warning leaks do not seek medical attention and when they do, such headaches are commonly misdiagnosed; about 25–50% of patients with subarachnoid haemorrhage are initially misdiagnosed.[16] Misdiagnosis occurs because of failure to recognise the variable clinical presentations of subarachnoid haemorrhage, lack of knowledge regarding the temporally related sensitivity of CT, and failure to do and interpret cerebrospinal fluid tests correctly.[16]

Cerebral venous sinus thrombosis

About 2–10% of patients with cerebral venous sinus thrombosis (CVST) present with TCH as their predominant clinical sign.[26,27] Although headaches are common in patients with CVST, occurring in 75–95% of patients, they tend to be of a more gradual subacute onset.[28,29] The headaches of CVST are persistent and are exacerbated by transient increases in intracranial pressure that occur during coughing, sneezing, or other Valsalva manoeuvres. Headaches can also worsen when in the recumbent position and upon awakening. Although headaches are most commonly accompanied by other symptoms and signs of CVST including seizures, papilloedema, altered level of consciousness, and focal neurological symptoms or signs, 15–30% of patients present with an isolated headache.[27–28,30] Although these headaches most commonly have a gradual, subacute onset, TCH is the main symptom in about 2–10% of patients.[26,27] CVST is more common during puerperium and these patients more commonly have an acute presentation that may include TCH.[31] Patients with CVST who present with TCH are clinically indistinguishable from patients presenting with TCH caused by subarachnoid haemorrhage. Headache in CVST can be caused directly by distention of veins or sinuses, increased intracranial pressure, or associated ischaemic or haemorrhagic stroke.[32]

Initial assessment for suspected subarachnoid haemorrhage, including brain CT and lumbar puncture, is commonly inadequate for the diagnosis of CVST. In patients with normal results on neurological examination, brain CT is normal in about 25%. In those with focal neurological deficits, there are CT abnormalities in about 90%.[33,34] CT abnormalities can include venous infarcts, evidence of oedema, or hyperdensity within the occluded sinus. However, subtle findings on CT can be easily misinterpreted. For example, thrombus in a cerebral vein can be mistaken for a subarachnoid haemorrhage.[35] Abnormalities detected by lumbar puncture that support a diagnosis of CVST are present in only some patients. About 50% of patients have a combination of high red-blood-cell count, high protein, and lymphocytic pleocytosis, or high opening pressure.[36,37] MRI with venography is commonly needed for the diagnosis of CVST and should

be considered whenever there is clinical suspicion for this disorder (figure 1).

Cervical artery dissection

Headache is the most common symptom in patients presenting with cervical artery dissection. Headache is reported by 60–95% of patients with carotid artery dissections and in about 70% of patients with vertebral artery dissections.[38] Although headaches most commonly have a gradual onset, 20% of patients present with TCH.[39] According to the International Headache Society's diagnostic criteria, headaches secondary to cervical artery dissection must be ipsilateral to the dissected artery.[40] Headaches due to carotid-artery dissection are invariably ipsilateral to the dissection and most commonly involve the jaw, face, ears, periorbital, and frontal or temporal region. Headaches due to vertebral-artery dissection are commonly located in the occipital-nuchal region; however, with dissection of either artery, headaches may less commonly be diffuse and bilateral.[41] Neck pain accompanies head pain in 50% of patients with vertebral-artery dissection and 25% of patients with carotid-artery dissection.[38] Although patients with cervical-artery dissection rarely present with headache or neck pain in the absence of other neurological symptoms and signs, headache can precede other neurological manifestations. In such cases, the median time from onset of headache to onset of other neurological symptoms is 4 days with carotid dissection and 14·5 h with vertebral dissection.[38] Associated neurological symptoms and signs include amaurosis fugax, Horner's syndrome, pulsatile tinnitus, dysgeusia, diplopia, or other stroke manifestations.

Further enforcing the need for a comprehensive diagnostic assessment, brain CT and lumbar puncture are usually normal in patients with cervical-artery dissection in the absence of ischaemic stroke. Additional testing for diagnosis should include ultrasound, CT angiography, magnetic resonance angiography, conventional angiography, or MRI of the neck with a fat-saturation protocol (technique of suppressing adjacent fat; figure 2).

Acute hypertensive crisis

Patients with acute hypertensive crisis and posterior reversible leucoencephalopathy syndrome may rarely present with TCH. There are two case reports[42,43] in which TCH was a prominent presenting feature of a hypertensive crisis or posterior reversible leucoencephalopathy syndrome. In one of these cases, a patient presented with hypertension, TCH, and MRI changes without other features of a hypertensive crisis or posterior reversible leucoencephalopathy syndrome.[42] In the other case, the patient had generalised seizure activity in addition to recurrent TCH.[43] Diffuse, segmental vasospasm involving arteries of the circle of Willis and its branches was detected by angiography.

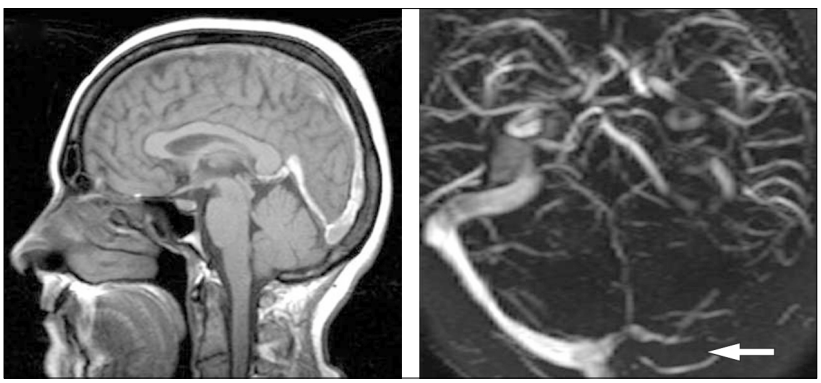

Figure 1: **Cerebral venous sinus thrombosis**
Left: T1 weighted sagittal MRI reveals hyperintense signal within the superior sagittal sinus and straight sinus. Right: Magnetic-resonance venogram reveals loss of flow signal secondary to thrombus in the central portion of left transverse sinus (arrow).

About 20% of patients with hypertensive crises have associated headaches. However, most of these are not consistent with TCH.[44] The head pain associated with acute hypertensive crises can be the direct result of increased pressure stimulating the sensory afferents that innervate the larger intracranial arteries.[45] Acute hypertensive headaches are commonly located in the posterior head, probably because of the greater density of sensory afferents from C-2 (the second cervical vertebra) that supply the posterior circulation. During hypertensive crises, symptoms other than headache are typically present including dizziness, dyspnoea, chest pain, psychomotor agitation, focal neurological deficits, and epistaxis.[44] Hypertensive emergencies are associated with end-organ damage, which most commonly includes stroke, acute pulmonary oedema, and hypertensive encephalopathy.

Posterior reversible leucoencephalopathy syndrome presents as headache, seizures, and visual loss, commonly in the setting of extreme hypertension. Headache caused by posterior reversible leucoencephalopathy syndrome

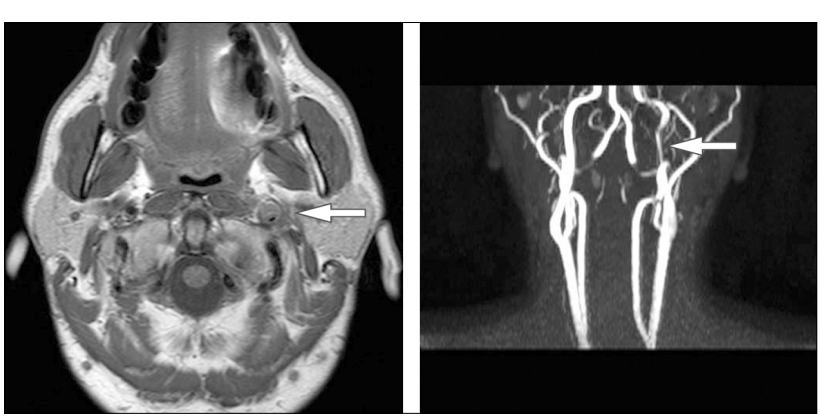

Figure 2: **Cervical artery dissection**
Left: Axial FLAIR MRI reveals a false lumen and crescent sign in the left internal carotid artery (arrow). Right: Gadolinium bolus magnetic resonance angiogram reveals tapered stenosis of the mid-cervical portion of the left internal carotid artery.

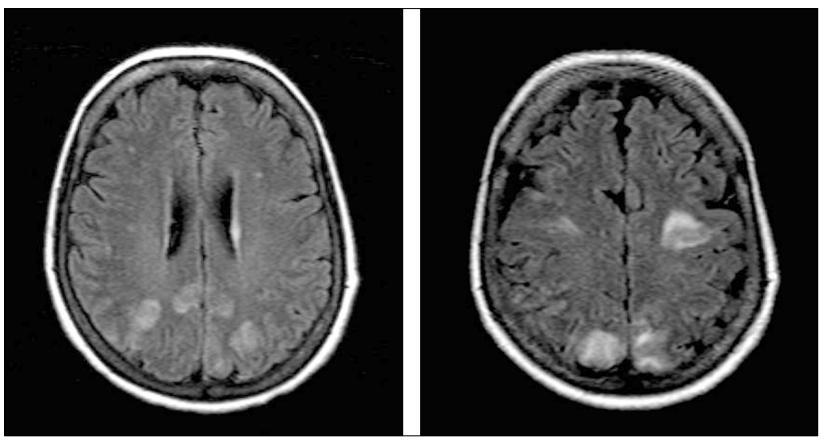

Figure 3: Axial FLAIR MRI showing posterior reversible leucoencephalopathy
These images show a relatively symmetrical hyperintense signal involving both grey and white matter of the occipital, parietal, and posterior frontal brain; outside the distribution of a single vascular territory. Also note the relative absence of deep white-matter lesions typically seen in patients with primary angiitis of the CNS.

generally has an acute onset. Patients may have associated nausea and vomiting, altered mental status, and focal neurological signs.[46,47] Posterior reversible leucoencephalopathy syndrome can also occur in the setting of disorders other than hypertension including eclampsia, thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome, and ciclosporine neurotoxicity.[48] Although neurological deficits are reversible in most patients with posterior reversible leucoencephalopathy syndrome, a few may have permanent clinical sequelae due to infarction or haemorrhage.[49]

Acute hypertensive crises and posterior reversible leucoencephalopathy syndrome can be easily overlooked in a patient presenting with TCH. In such cases, hypertension might be misconstrued as part of a stress response, secondary to TCH. Testing for subarachnoid haemorrhage with CT and lumbar puncture is unlikely to aid a proper diagnosis. However, MRI can show evidence of oedema involving the posterior white matter and cortex, commonly involving the parietal and occipital lobes, and potentially spreading to the basal ganglia, brainstem, and cerebellum (figure 3).[50] Because early imaging abnormalities are secondary to vasogenic oedema, as opposed to ischaemia or infarction, prompt diagnosis is essential in order to treat while the condition is most reversible.[51]

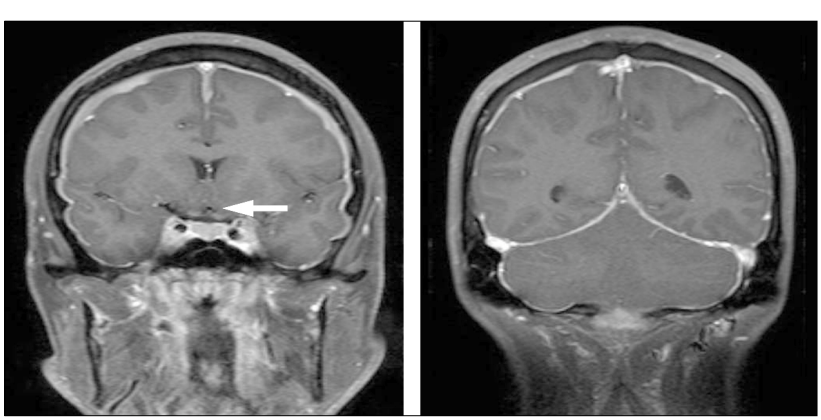

Figure 4: **Coronal T1-weighted brain MRI of a patient with spontaneous intracranial hypotension**
The gadolinium reveals diffuse and contiguous thickening and enhancement of the pachymeninges, engorged venous sinuses, and descent of the optic chiasm (arrow).

Spontaneous intracranial hypotension

Spontaneous intracranial hypotension usually appears as a positional headache that worsens when upright and improves after lying down. Sponataneous intracranial hypotension is typically preceded by minor trauma such as trivial falls, lifting, coughing, and sports activities. Most headaches are bilateral, in the frontal, fronto-occipital, holocephalic, or occipital regions, and can be associated with throbbing.[52] However, about 15% of patients with spontaneous intracranial hypotension present with TCH. A study[53] of 28 patients with spontaneous intracranial hypotension, identified four who presented with TCH. In a second study,[54] four of 24 patients with spontaneous intracranial hypotension presented with TCH. Other features of spontaneous intracranial hypotension that usually accompany headaches include nausea, vomiting, neck stiffness or pain, auditory muffling, tinnitus, dizziness, diplopia, visual blurring, interscapular pain, or upper-extremity radicular pain.

In patients with spontaneous intracranial hypotension, TCH in the presence of neck pain and stiffness can easily be misconstrued as evidence of subarachnoid haemorrhage. Assessment for suspected subarachnoid haemorrhage, including brain CT and lumbar puncture can provide supporting evidence for spontaneous intracranial hypotension but is usually non-diagnostic. When lumbar puncture is done because of suspicion of other processes, opening pressure is typically low and can even be undetectable. Cerebrospinal fluid is generally clear and colourless, protein concentration is normal or slightly high (less than 100 mg/dL), erythrocyte count can be normal or high, a lymphocytic pleocytosis up to 50 cells per mm^3 is common, and results of glucose, cytological, and microbiological tests are normal.[55] Brain MRI with gadolinium typically reveals features of spontaneous intracranial hypotension including diffuse pachymeningeal gadolinium enhancement and evidence of "brain sag" or cerebellar tonsillar descent (figure 4). Crowding of the posterior fossa, reduction in the prepontine space, descent of the optic chiasm, and subdural collections may also be present. MRI of the spine might show extraarachnoid cerebrospinal fluid collection. Nuclear cisternography, CT myelography, or magnetic resonance myelography might be necessary to confirm the presence and location of the cerebrospinal fluid leak.

Ischaemic stroke

TCH has been reported as a presenting feature of ischaemic stroke. Headaches occur in about 25% of

patients with stroke, half of which develop before the onset of other stroke manifestations.[56] In patients with a history of a primary headache disorder, headaches occurring at the time of ischaemic stroke commonly resemble their usual headaches. In patients without such a history, a throbbing headache ipsilateral to the stroke is most common.[57] Appearance of headache with ischaemic stroke varies with the severity, location, and duration of ischaemia as well as risk factors including a history of migraine, patient age, and genetic background.[58] Headache is more common with large ischaemic stroke, in the territory of the posterior circulation, in patients with a history of migraine, and those of a young age.[56,59] Although most patients with stroke-related headaches do not present with TCH, three such patients have been reported and one case of TCH as the primary clinical feature of embolic bilateral cerebellar infarcts has been reported.[2,60] Initial studies for subarachnoid haemorrhage are commonly non-diagnostic in patients with recent strokes, providing further evidence for the necessity of MRI in patients with TCH.

Retroclival haematoma

Patients with retroclival haematomas can present with TCH. Retroclival haematoma is a rare symptom of severe head and neck injuries that result in atlantoaxial dislocation.[61,62] Spontaneous haemorrhage, although even more rare, can occur, and might be secondary to dural-based arteriovenous fistulae and meningeal tumours.[63]

Two patients with spontaneous haemorrhage have been reported, both of whom presented with a TCH and normal results on neurological examination and cerebral angiography.[64,65] Cerebrospinal fluid analysis and MRI were essential in establishing the proper diagnosis. Although the optimum radiological approach for the diagnosis of a spontaneous retroclival haematoma has not been clearly established, MRI imaging with gadolinium and cerebral angiography with selective external carotid artery injection have been recommended.[65]

Pituitary apoplexy

Pituitary apoplexy is haemorrhage or infarction of the pituitary gland, usually in the setting of a pituitary adenoma. Although pituitary apoplexy is rarely encountered in the clinical setting, autopsy evidence of infarction of more than 25% of the pituitary gland is found in 1–3% of the population.[66] Apoplexy can occur in association with pregnancy, general anaesthesia, bromocriptine therapy, and pituitary irradiation, but most commonly occurs in patients with no known history of a pituitary tumour.[67] There is a wide variation in the severity of clinical symptoms in patients with pituitary apoplexy; this ranges from relatively mild symptoms, to adrenal crisis, coma, and sudden death. Patients with pituitary apoplexy most commonly present with a combination of acute headache, nausea, decreased visual acuity, ophthalmoplegia, and reduction in visual fields.[68] Headache, usually of sudden and severe onset, is the most common presenting symptom and can be the predominant presenting feature.[68] Cases of pituitary apoplexy in patients presenting with TCH and normal physical examinations, CT scans, and cerebrospinal fluid have been reported.[69,70] Because pituitary tumours are isodense to normal brain tissue on CT, they can easily be overlooked if MRI is not also done.

Third-ventricle colloid cyst

Patients with colloid cysts of the third ventricle can present with TCH. These tumours account for 0·5% of intracranial tumours, affect men more often than women, and are most commonly diagnosed between the third and fifth decades of life.[71] Headache is the most common symptom of a third ventricular colloid cyst and is reported by 68–100% of diagnosed patients.[72] The headache typically begins abruptly, endures for seconds to one day, and then resolves quickly.[73] These headaches are most commonly located in the bilateral frontal, frontoparietal or fronto-occipital regions.[74] The pain is typically severe and can be relieved by recumbency; 50% of patients have associated nausea and vomiting. Loss of consciousness, changes in cognition, seizures, coma, and death can occur.[72] The diagnosis of colloid cyst is made by CT or MRI.

Intracranial infection

Although onset of headache associated with bacterial or viral meningitis is typically gradual, TCHs have been reported. A prospective analysis[3] of patients with TCH in primary-care practices, identified four of 148 patients who had an infectious cause. CSF examination is essential for the diagnosis of these cases.

RCVS

TCH might be associated with diffuse, segmental, reversible cerebral vasoconstriction.[75–78] In such cases, angiography shows alternating segments of vasoconstriction and dilation in the proximal and distal branches of the circle of Willis.

The term RCVS describes a group of disorders characterised by reversible segmental cerebral vasoconstriction. These disorders include TCH with vasosconstriction, benign angiopathy of the CNS, Call-Fleming syndrome, postpartum angiopathy, and drug-induced vasospasm.[79–81] Cases of RCVS have historically been named according to a patient's medical history, time of onset of symptoms and the specialty of the physician caring for the patient. Despite different nosology, these patients present with TCH, normal or near normal cerebrospinal-fluid examination, and reversible cerebral segmental vasoconstriction involving arteries of the circle of Willis. Patients with RCVS may differ in regards to the presence and severity of neurological deficits and imaging abnormalities. Patients

can present with isolated TCH or TCH in conjunction with altered cognition, motor and sensory deficits, seizures, visual disturbances, ataxia, speech abnormalities, nausea, and vomiting.

RCVS must be considered in patients who present with TCH, vasoconstriction of one or more arteries of the circle of Willis that reverses, and normal or near-normal cerebrospinal-fluid. Cases of RCVS have been reported in patients with a history of migraine, women in the postpartum period, and in people exposed to different drugs including ergotamine, triptans, selective serotonin reuptake inhibitors, pseudoephedrine, cocaine, amphetamines, methylenedioxymethamphetamine (ecstasy), and bromocriptine.[82–113]

Given the presence of segmental cerebral vasoconstriction, a key component in the diagnosis of RCVS is the differentiation of this disorder from primary angiitis of the CNS (PACNS). This is essential to avoid the unnecessary use of long-term immunosuppressants and cytotoxic drugs in patients with RCVS. Distinguishing features can be found in the patient history and in laboratory and radiological assessment. The most helpful clinical feature that distinguishes these two entities is the acuity of onset of the headache and other clinical symptoms. Patients with PACNS do not have TCH, except in the rare circumstance of a ruptured intracranial aneurysm associated with the vasculitis. In addition, PACNS presents as an insidious and progressive neurological disease over weeks to months with the potential for step-wise deterioration based on the focal deficits that can accumulate as the result of cerebral infarction. By contrast, patients with reversible cerebral angiopathy have an apoplectic onset with TCH. Laboratory assessment of patients with primary angiitis of the CNS commonly reveals systemic abnormalities including changes in haemoglobin, white-blood-cell count, and sedimentation rate.[114] These abnormalities are generally not seen with nor attributed to RCVS. Results of cerebrospinal fluid analysis are notably abnormal in about 80% of patients with primary angiitis of the CNS and are normal or near normal in patients with RCVS.[113] Brain MRI in patients with PACNS typically reveals multifocal lesions in the deep white matter and cortical infarctions in the distribution of separate vascular territories. Indeed, a completely normal MRI, including diffusion and perfusion sequences, is very uncommon in patients with symptomatic primary angiitis of the CNS.[115–118] By contrast, MRI can be normal in patients with RCVS. However, abnormalities consistent with posterior reversible leucoencephalopathy or watershed infarctions in the distal vascular territory of cerebral vessels with severe spasm have been described.[119] RCVS cannot be differentiated from PACNS by a single vascular imaging study. However, in patients with RCVS, substantial improvement in vasospasm, even in the absence of specific treatment, is expected within 4 weeks of symptom onset. Several months might be needed for complete normalisation of vascular imaging. On the other hand, vascular imaging abnormalities in patients with PACNS rarely normalise completely.

Primary cough, exertional, and sexual headache

Patients who present with acute onset of severe headache occurring only after precipitation by cough, physical exertion, or sexual activity and with a normal comprehensive assessment for causes of secondary headache, can be classified as having primary cough, exertional, or sexual headache. Just as with primary TCH, these diagnoses require a normal diagnostic assessment, as headaches precipitated by such manoeuvres might be secondary to many of the previously discussed causes of TCH as well as other structural abnormalities such as Chiari malformation type I.[120] The International Headache Society's diagnostic criteria stipulate that primary cough headache be precipitated by coughing, straining, or Valsalva, has sudden onset, and a duration of 1 s to 30 min.[40] Primary exertional headache can be brought on by any form of exercise, must be pulsating, and lasts from 5 min to 48 h.[40] The primary sexual headaches are divided into those occurring preorgasmic and those occurring with orgasm. The orgasmic headaches are of the thunderclap variety whereas most preorgasmic headaches present as a dull ache in the head and neck that increases with sexual excitement.[40]

Primary TCH

Patients with TCH in whom an underlying cause is not found are diagnosed with primary TCH. Primary TCH is a diagnosis of exclusion, which can be made only after exhaustive assessment for all possible underlying causes. Primary TCH has a relatively benign prognosis. This headache disorder is indistinguishable and is probably the same entity that has been previously described as benign TCH, idiopathic TCH, benign vascular headache, migrainous vasospasm, and crash migraine.[121–128]

The International Headache Society's diagnostic criteria stipulate that the head pain of primary TCH must be severe, sudden in onset, reach maximum intensity in less than 1 min, and last from 1 h to 10 days (panel 2).[40] Although headache can recur within the first week after onset, it should not recur regularly over subsequent weeks or months.[40] Normal cerebrospinal fluid assessment and brain imaging are also needed.

Pathophysiology

The pathophysiology of primary and secondary TCH is not well understood. However, it is possible that secondary TCH may be caused by direct activation of intracranial pain-sensitive structures, especially the cerebral blood vessels.

The sympathetic nervous system may play an important part in the pathophysiology of primary TCH and secondary TCH, including RCVS. The proximal portions

Panel 2: **The International Headache Society's diagnostic criteria for primary TCH**

A. Severe head pain fulfilling criteria B and C
B. Both of the following characteristics:
sudden onset, reaching maximum intensity in <1 min, lasting from 1 h to 10 days
C. Does not recur regularly over subsequent weeks or months
D. Not attributed to another disorder (normal cerebrospinal fluid and normal brain imaging are needed)

of the large intracranial arteries are innervated by neuropeptide Y and noradrenaline containing sympathetic afferents, which modulate vascular tone.[129,130] A heightened response to endogenous circulating catecholamines, exaggerated stimulation of sympathetic receptors by exogenous drugs, or abnormal antidromic discharge of sympathetic afferents (autonomic dysreflexia) could cause acute vasoconstriction or alterations in vascular tone that result in the production of head pain.

A pivotal role of the sympathetic nervous system is supported by several experimental and clinical lines of evidence. Altered sympathetic receptor sensitivity is thought to be responsible for the delayed cerebral vasospasm reported after subarachnoid haemorrhage. The severity and duration of experimental vasospasm decreases after bilateral cervical sympathectomy.[131] Finally, the role of the cerebrovascular sympathetic nervous system is highlighted by the clinical examples of TCH occurring in patients with pheochromocytoma, acute hypertensive crises, eclampsia, and sympathomimetic drug use and intoxication.[132–136]

Diagnostic assessment

TCH must be managed as a medical emergency in order to avoid potentially catastrophic consequences that can occur with secondary TCH (figure 5). The initial diagnostic assessment must be focused on ruling out subarachnoid haemorrhage. Non-contrast CT of the brain, the first test in this assessment, is highly sensitive and specific for the diagnosis of subarachnoid haemorrhage when done in close temporal relationship to the onset of symptoms. During the first 12 h after the onset of headache, third generation CT scanners have a specificity of 98% and a sensitivity that nears 100%.[16] However, this specificity and sensitivity assumes interpretation by highly trained neuroradiologists. When interpreted by less experienced clinicians, CT sensitivity is probably lower. In addition, the sensitivity of CT for the detection of subarachnoid haemorrhage declines with increasing duration from haemorrhage onset, reaching 86% on day two, 76% after 2 days, and 58% after 5 days.[137] Therefore, cerebrospinal fluid assessment is needed in patients who present with TCH and have normal or non-diagnositic CT scans.

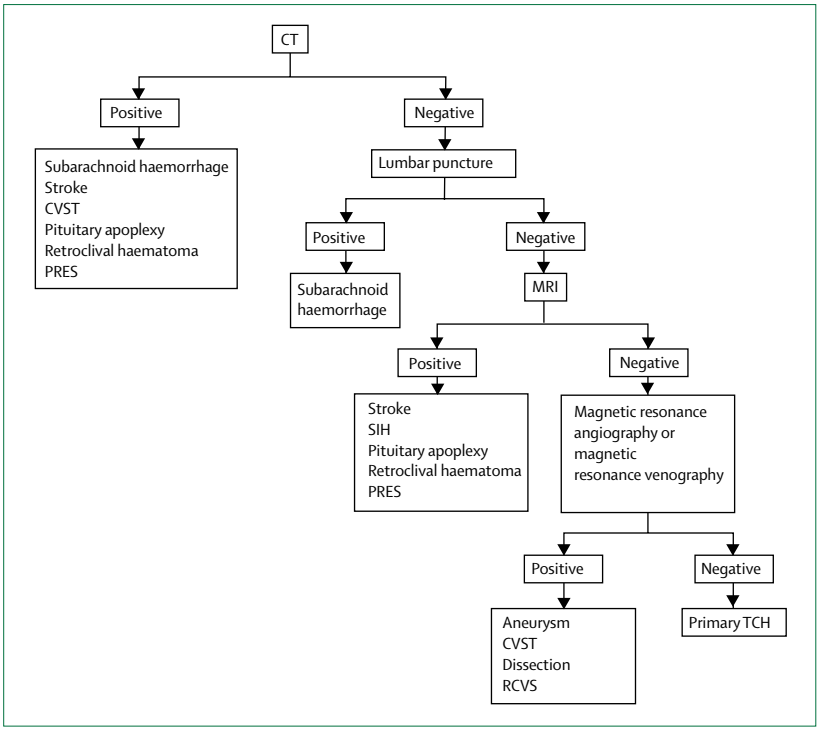

Figure 5: **Initial assessment of TCH**
Basic testing to be considered for the assessment of TCH. Additional testing might be necessary according to clinical presentation and assessment findings. In certain circumstances, when CT, lumbar puncture, and magnetic resonance angiography are negative, but the index of suspicion for an intracranial aneurysm is very high, four-vessel digital subtraction angiography can also be indicated. Patients with subarachnoid haemorrhage or posterior reversible leucoencephalopathy syndrome (PRES) should also undergo angiography to assess for the possibility of vasospasm. SIH=spontaneous intracranial hypotension.

Measurement of routine cell counts, protein, glucose, opening pressure, and inspection for xanthochromia should be done. Because visual inspection for xanthochromia is associated with a high rate of false negative interpretation, perhaps up to 50% of samples, spectrophotometry should be done when available. Spectrophotometry also helps to overcome the problem of false positives, which can occur when cerebrospinal fluid is not promptly centrifuged and examined, and with traumatic taps. Analysis for bilirubin by spectrophotometry has a sensitivity that nears 100% when lumbar puncture is done 12 h to 2 weeks after subarachnoid haemorrhage.[21]

MRI should be done in patients with TCH who have normal or non-diagnostic CT scans and cerebrospinal fluid analysis. Although MRI might not be available in all medical settings on an emergency basis, imaging should be done as soon as possible. MRI will often be necessary to diagnose many of the possible causes of TCH such as unruptured intracranial aneurysm, stroke, spontaneous intracranial hypotension, pituitary apoplexy, retroclival haematoma, posterior angiopathy of the CNS, CVST, cervical artery dissection, and reversible cerebral angiopathy. A diagnosis of primary TCH should not be made in the absence of normal MRI. In most cases,

magnetic-resonance studies should include cerebral MRI, magnetic resonance angiography, magnetic resonance venography and, if necessary, MRI of the cervical arteries with fat saturation technique. CT angiography can be used instead of magnetic resonance angiography for the diagnosis of intracranial aneurysm. The sensitivity of magnetic resonance angiography for the detection of intracranial aneurysms depends on the size of the aneurysm, but ranges from 69% to 100%.[138] When aneurysms are 6 mm or larger, the sensitivity of magnetic resonance angiography is greater than 95%. CT angiography, which has been studied less extensively with regards to its value in the diagnosis of intracranial aneurysm, is thought to have a detection rate of 85–98%.[139,140]

Evidence suggests that conventional angiography is not a necessary component in the assessment of patients with TCH, normal neurological examinations, and normal CT and lumbar puncture. Both retrospective and prospective analyses of these patients have shown favourable outcomes. A retrospective study[141] of 71 patients with TCH and normal CT and lumbar puncture found no patients with subarachnoid haemorrhage during an average follow-up of 3·3 years. A study of 225 patients with primary TCH in four prospective studies found no patients with subarachnoid haemorrhage or sudden death during at least the next year after onset of headache.[142–145] In addition, conventional angiography is not risk-free, with a 1% prevalence of transient complications and a 0·5% prevalence of permanent neurological complications. The risk of angiography might be even higher in patients with TCH, especially if there is associated vasospasm.[146,147] Given overwhelming evidence for benign outcomes in patients with TCH, who have normal results on neurological examination, CT, and lumbar puncture, conventional angiography is not currently recommended as part of the standard assessment of these patients. However, in highly selected cases when the clinical suspicion for intracranial aneurysm remains high despite normal or non-diagnostic CT, lumbar puncture, and MRI studies, conventional angiography might still be considered.

Conclusion

All patients with TCH must be assessed urgently and several different causes must be considered. Initial diagnostic studies should include an unenhanced brain CT, and, if normal or non-diagnostic, a lumbar puncture. In circumstances where both studies are normal, further diagnostic assessment with MRI, magnetic resonance angiography of the brain and neck, and magnetic resonance venography is necessary. Primary TCH is a diagnosis of exclusion and can therefore only be made if the results of these studies are normal. When this assessment reveals reversible segmental vasoconstriction, normal or near-normal cerebrospinal fluid studies, and a lack of any other underlying pathology, the patient should be classified as having reversible vasoconstriction syndrome.

Search strategy and selection criteria

References for this review were identified by searches of MEDLINE and PubMed between 1966 and April 2006, and references from relevant articles. Articles were also identified through searches of the authors own files. Searches were done with a combination of the terms "thunderclap headache", "sentinel headache", "warning headache", "subarachnoid hemorrhage", "intracranial thrombosis", "vertebral artery dissection", "carotid artery diseases", "central nervous system vasculitis", "intracranial vasospasm", "puerperal disorders", "cerebrovascular accident", "posterior reversible encephalopathy syndrome", "reversible posterior leukoencephalopathy", "spontaneous intracranial hypotension", "pituitary apoplexy", "benign angiopathy of the central nervous system", "migrainous vasospasm", and "Call-Fleming syndrome". Abstracts and reports from meetings were also included. Only papers published in English were reviewed. The final reference list was generated based on originality and relevance to the topics covered in the review.

Contributors
All authors contributed to the literature search, figures, and writing of the manuscript.

Conflicts of interest
We have no conflicts of interest relevant to this article.

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