Current Pain and Headache Reports (2024) 28:73–81
https://doi.org/10.1007/s11916-023-01202-6

CHRONIC PAIN MEDICINE (O VISWANATH, SECTION EDITOR)

# Ominous Causes of Headache

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Accepted: 6 December 2023 / Published online: 13 December 2023


## Abstract

**Purpose of Review** While primary headaches like migraines or cluster headaches are prevalent and often debilitating, it's the secondary headaches—those resulting from underlying pathologies—that can be particularly ominous. This article delves into the sinister causes of headaches, underscoring the importance of a meticulous clinical approach, especially when presented with red flags.

**Recent Findings** Headaches, one of the most common complaints in clinical practice, span a spectrum from benign tension-type episodes to harbingers of life-threatening conditions. For the seasoned physician, differentiating between these extremes is paramount.

**Summary** Headache etiologies covered in this article will include subarachnoid hemorrhage (SAH), cervical artery dissection, cerebral venous thrombosis, meningitis, obstructive hydrocephalus, and brain tumor.

**Keywords** Headache · Subarachnoid hemorrhage · Cervical artery dissection · Hydrocephalus · Cerebral venous thrombosis · Meningitis

## Introduction

In the vast landscape of clinical medicine, headaches, often perceived as mundane, can sometimes be the sentinel of grave underlying pathologies. While the majority of headaches encountered in daily practice are primary and benign, a subset veers into the realm of the ominous, heralding conditions that can be life-altering or even life-threatening. For the sophisticated physician, the challenge is not merely to diagnose and treat but to discern the subtle cues that differentiate the benign from the sinister. This article seeks to shed light on the world of ominous headaches, emphasizing the importance of a nuanced approach in their evaluation and management.

The term "headache" is deceptively simple, yet its clinical implications are vast and varied. From the throbbing pain of a migraine [1] to the piercing intensity of a cluster headache [2], the spectrum is broad. However, nestled within this spectrum are headaches that serve as harbingers of conditions that demand immediate attention. These are the headaches that keep the astute clinician vigilant, the ones that underscore the adage, "common things are common, but do not be fooled by the uncommon."

Consider the sudden, thunderclap onset of a headache that reaches peak intensity within minutes. To the informed physician, this is a red flag, a potential sign of a subarachnoid hemorrhage, where every moment of delay in diagnosis can have profound implications for patient outcomes [3]. Or ponder upon the new headache in an elderly patient, localized and associated with jaw claudication or visual disturbances. This could be the whisper of giant cell arteritis, where the stakes are as high as irreversible blindness [4].

Then there are the more elusive presentations. The young woman with daily, persistent headaches, pulsatile tinnitus, and transient visual obscurations, potentially signaling idiopathic intracranial hypertension [5]. Or the individual with a recent history of minor neck trauma or chiropractic

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manipulation, now presenting with unilateral neck pain and neurological deficits, raising the specter of a cervical artery dissection [6–8].

The world of ominous headaches is not limited to vascular pathologies. Central nervous system infections [9] space-occupying lesions like tumors [10] or abscesses, and conditions like pituitary apoplexy all stake a claim in this domain [11]. Each presents its own set of challenges, its own set of clues, demanding a synthesis of clinical acumen, investigative prowess, and therapeutic precision.

For the seasoned physician, the journey into the realm of ominous headaches is a testament to the art and science of medicine. It is a reminder that medicine is not just about knowledge but about insight, not just about diagnosis but about discernment. It underscores the importance of holistic patient evaluation, where a detailed history often holds more value than a battery of tests. It is a call to always remain a student, to continuously refine one's clinical skills, and to approach each patient with both humility and confidence.

In the ensuing discourse, we will delve deeper into the intricacies of these ominous headaches, exploring their clinical presentation, diagnostic challenges, and management nuances. As we embark on this journey, let it be a reminder of the profound responsibility that rests upon the shoulders of the physician, the responsibility to see beyond the obvious, to listen to the unsaid, and to act with both compassion and competence.

## Headache from Subarachnoid Hemorrhage

Subarachnoid hemorrhage is a life-threatening condition characterized by bleeding into the subarachnoid space, which is the area between the arachnoid membrane and the pia mater surrounding the brain. It can be traumatic, or spontaneous. The latter are most commonly due to aneurysms, and women have 1.3 × higher relative risk (RR) compared with men [12].

The classic presentation of SAH is the sudden onset of a severe headache, often described as the "worst headache of my life." This headache is typically of maximal intensity at onset [13]. This is accompanied by nausea, vomiting, photophobia, and sometimes loss of consciousness. Neck stiffness or pain, due to meningeal irritation, can also be a presenting symptom. In severe cases, patients may present with seizures or focal neurological deficits [14, 15]. Several risk factors have been identified for SAH. These include: hypertension [12, 14], smoking (risk is dose-dependent), alcohol consumption, a family or personal history of SAH or cerebral aneurysms, a history of polycystic kidney disease or Ehlers-Danlos syndrome [16]. The most important modifiable risk factor are blood pressure control and smoking cessation. Family history is the most important non modifiable risk factor. Persons with 2 or more relatives with aneurysmal SAH should be screened every 5–7 years with brain imaging [12].

The severity of SAH can be graded using the Hunt and Hess or World federation of Neurological surgeons scoring systems. The gold standard for diagnosing SAH is a non-contrast computed tomography (CT) scan of the brain, which can detect fresh blood in the subarachnoid space. If the CT is done within 6 h of headache onset, then a negative result is sufficient to exclude SAH in patients who do not have a new neurological deficit. For patients who present after 6 h of symptom onset or who have a new neurologic deficit, a negative brain CT may not reliable exclude a SAH and in these instances a lumbar puncture is done to look for xanthochromia (yellow discoloration of the cerebrospinal fluid), which is indicative of SAH [17]. If SAH is confirmed, cerebral angiography is performed to identify the source of the bleed, most commonly a cerebral aneurysm. Digital subtraction angiography should be performed in equivocal cases. Magnetic resonance imaging (MRI) can also be useful in certain cases, especially when vascular malformations are suspected.

The primary goal in the treatment of SAH is to prevent rebleeding and manage complications.

While aggressive blood pressure reduction can compromise cerebral perfusion, modest reduction can prevent rebleeding; thus a systolic BP target of 140–160 mmHg is recommended. Nimodipine is a calcium channel blocker has been shown to reduce the risk of cerebral vasospasm, a common complication following SAH. Prophylactic antiseizure medication should not be routinely used for new onset seizure after SAH [12]. Rather, they can be considered in high-risk patients such as those with ruptured middle cerebral artery aneurysm, intraparenchymal hemorrhage, high-grade aneurysmal SAH, hydrocephalus, or cortical infarction.

Once SAH is confirmed, prompt neurosurgical or neurointerventional consultation is vital. Definitive management may involve surgical clipping or endovascular coiling of the aneurysm. Patients should be admitted to an intensive care setting as risk of re-bleeding is highest within the first 24 h. Delayed cerebral ischemia is a significant complication in many cases and is thought to be caused by a combination of myriad brain injury processes triggered by aneurysm rupture and early brain injury [18].

## Headache from Cervical Artery Dissection

Cervical artery dissection (CAD) encompasses both carotid and vertebral artery dissections. It represents a significant cause of ischemic stroke, especially in younger adults. CAD involves a tear in the arterial wall, leading to the formation of an intramural hematoma, which can result in arterial stenosis, occlusion, or embolism. Internal carotid artery dissections (ICAD)

are 3.5 × more common than vertebral artery dissections (VAD). Together, ICAD and VAD account for ~ 20% of ischemic strokes in patients under the age of 40 years. It is also a major cause of cerebrovascular injury in children, occurring in 20% of cases of pediatric acute ischemic stroke [19] A history of trauma is elicited in 40% of cases. The trauma can be minor, including sudden movements such as those from chiropractic manipulations, vigorous physical activities, peripartum Valsalva, or intense sneezing or coughing. A history of unliteral headache with or without neck pain is elicited 65% of the time.

Patients with ICAD can present with an incomplete painful Horner's syndrome (ptosis, miosis, and anhidrosis), [20]. Approximately 45% will have an audible carotid bruit or pulsatile tinnitus. Upto 10% can have a CN palsy, with the most common CN palsy being the hypoglossal nerve [21]. 6–38% experience transient monocular visual loss [22]. Additionally, symptoms of ischemic stroke, such as hemiparesis, facial droop, or aphasia, may manifest due to embolization from the dissected artery.

Patients with VAD will present with headache in the occipital scalp and posterior neck. The neck pain can be bilateral 30–60% of the time [23]. Signs of posterior circulation ischemia include: vertigo, vertical nystagmus, limb ataxia, dysphagia, hoarsens, ipsilateral arm, trunk or leg weakness, and contralateral loss of pain and temperature sensation.

In addition to trauma, other risk factors include connective tissue and collagen vascular disorders such as Ehlers-Danlos syndrome, Marfan syndrome, and Fibromuscular dysplasia, infection, and family history.

Firstline imaging per the American Heart Association is CTA or MRI with fat suppression/MRA [24]. Findings consistent with arterial dissection include a double lumen, intraluminal hematoma (crescent sign), long tapered arterial stenosis, a pseudoaneurysm, and medial or subendothelial hemorrhage. The string sign, also known as the carotid string sign or slim sign**,** refers to the thin string of intravascular contrast material distal to a stenotic focus in ICAD, caused by decreased pressure and flow distal to the stenosis, which causes a collapse of the distal internal carotid artery [25].

The primary treatment for CAD, in the absence of contraindications, involves anticoagulation (e.g., heparin transitioning to warfarin or direct oral anticoagulants) or antiplatelet agents (e.g., aspirin or clopidogrel) to prevent thromboembolic events. There is no consensus as to which agent is better, but in general anticoagulants are avoided in intracranial dissections. In addition to heparin, direct oral anticoagulants are another option, but data on their use with dissections is limited. As with SAH, blood pressure shoud be maintained below 140–160 mmHg to prevent exacerbation of the dissection.

## Headache from Brain Tumors

Headache due to tumor may be caused by direct pressure or traction on structures that are sensitive to pain like the cranial nerves, meningeal arteries, venous channels of the brain, or parts of dura matter or, skin and subcutaneous tissue or muscle [26]. The possibility that central sensitization and/or deficient brainstem inhibition may contribute to the pathogenesis of brain tumor headache is under debate. Acute headache can also occur from hydrocephalus due to increased intracranial pressure or from mass effect of the tumor. Hemorrhage into or around the tumor can also present with headache. It has been posited that the tumor itself may produce substances critical for the development of head pain. These may include nitric oxide synthase, calcitonin gene-related peptide, tumor necrosis factor alpha, vasoactive intestinal peptide and many others. In a recent study an increase of substance P and of prostaglandin E2 concentration within meningiomas was associated with higher preoperative pain intensity [26]. Dysfunctional descending pain-modulating circuits are believed to play an important role in the maintenance of prolonged headache pain. The possibility that central sensitization and/or deficient brainstem inhibition may contribute to the pathogenesis of brain tumor headache is still being debated. This may offer explanation as to why certain surgeries fail to relieve headache symptoms.

There is a greater likelihood of headache in children, in individuals with history of primary headache and in infratentorial and rapidly growing space-occupying lesions [26]. Metastasis of lung, breast cancer, malignant melanomas and carcinomas of the kidney and gastrointestinal tracts are the most frequent sources of metastatic brain tumors [27]. Gliomas, Meningiomas, pituitary adenomas are the primary intracranial tumors. While some reports suggest primary and metastatic brain tumors are equally likely to cause headaches [28], others suggest headache is more prevalent in primary and intracerebral tumor than in metastatic and extracerebral tumors. Headache may be influenced by pathology of the tumor and its location, but there is poor association between location of tumor and the location of headache [26]. Headache is more common with tumors below the tentorium cerebelli than supratentorial tumors. For example, slow growing low-grade supratentorial gliomas and meningiomas cause seizures more often than headaches. Independent of pathology, tumors in the posterior fossa [29–31] such as medulloblastomas and ependymomas, cause headache earlier in the clinical course. Tumors in this location tend to obstruct cerebrospinal fluid pathways early and lead to increased intracranial pressure causing more frequent headaches. Cerebello-pontine angle tumors like vestibular schwannomas present with hearing loss or tinnitus before onset of headache [32]. Headache associated with pituitary adenomas

and craniopharyngiomas are also accompanied by visual and endocrine symptoms [31, 32]. Characteristic paroxysmal thunderclap headache (sudden onset and resolution) can occur with third ventricular tumors like colloidal cysts which are known to cause acute obstructive hydrocephalus [33].

The International Headache Society has proposed diagnostic criteria [34] for headache attributed to brain tumors [Table 1].

MRI is the standard neuroimaging method used for diagnosis of brain tumors, for performing stereotactic biopsy, and for surgical planning in neuro-oncology [35]. Current evidence based data also suggest that radiolabeled amino acid PET or PET/CT is an accurate diagnostic method for several clinical indications including evaluation of suspicious brain tumors, glioma grading and delineation, detection of brain tumor recurrence and in providing useful prognostic information in patients with brain tumors [36, 37].

Glucocorticoids and non-opioid analgesics are used for treatment of headache related to tumors. Treatment of the brain tumor itself may involve chemotherapy, surgery, radiation therapy, or a combination and depends on tumor type, tumor location. Life expectancy is limited in metastatic brain tumors, and treatment is palliative. Treatment of brain tumors itself can cause headache. Radiotherapy can cause acute or chronic headaches stroke-like migraine attacks after radiation therapy. Stroke-like migraine attacks after radiation therapy (SMART) syndrome is rare but known condition in patients exposed to brain radiation [38]. Post-surgical post craniotomy headache is quite common. Finally, chemotherapy can cause headache [10].

## Headache from Cerebral Venous Thrombosis

Cerebral venous thrombosis (CVT) is a rare form of stroke that occurs when thrombosis in the dural venous sinuses occurs [39]. The most commonly involved sinus is the saggital sinus [Fig. 1]. CVT can lead to increased intracranial pressure and hemorrhagic infarcts. CVT should be especially considered in patients at risk, such as post or peripartum patients [11], and those with coagulopathies.

The clinical manifestations of CVT are highly variable, depending on the location and extent of the thrombosis. Headache is the most common symptom, present in up to 90% of cases, and may be diffuse or localized, often worsening over days to weeks. It can mimic a migraine or tension-type headache but typically is progressive and persistent. Other symptoms may include nausea and vomiting, visual disturbances (including papilledema due to increased intracranial pressure), seizures (which can be focal or generalized), focal neurological deficits, and altered consciousness ranging from drowsiness to coma [39].

CT plays a crucial role in the initial assessment of CVT [40]. The most direct sign of CVT on non-contrast CT is the visualization of a hyperdense thrombus within a dural sinus or cortical vein, often referred to as the "cord sign" when seen in a cortical vein, or the “hyperdense saggital sign” [41]. This finding is more common in the acute phase due to the high hematocrit of the clot. Diffuse cerebral swelling may be present, particularly if intracranial pressure is elevated. Parenchymal Lesions may also be seen, including edema or hemorrhagic infarctions, which can be bilateral and are often not confined to a single arterial territory. The distribution may suggest venous drainage patterns. On contrast CT, one may note the Empty Delta Sign [41], which is a filling defect in the sinus that appears as a triangular area of non-enhancement, surrounded by a rim of contrast-enhancing dura. However, this sign is not always present and may be absent in early or chronic stages. Occasionally, the thrombosed cortical veins may enhance with contrast due to the formation of collateral vessels around the thrombus. CT Venography (CTV) [40] provides a more detailed view of the cerebral venous system and can directly visualize a

**Table 1** International Headache Society diagnostic criteria for headache attributed to brain tumors.

A) Any headache fulfilling criterion C (below)

B) A space-occupying intracranial neoplasm has been demonstrated

C) Evidence of causation demonstrated by at least two of the following:

- Headache has developed in temporal relation to the intracranial neoplasia, or led to its discovery
- Either or both of the following:
- Headache has significantly worsened in parallel with worsening of the neoplasm
- Headache has significantly improved in temporal relation to successful treatment of the neoplasm
- Headache has at least one of the following four characteristics:
  - Progressive
  - Worse in the morning and/or when lying down
  - Aggravated by Valsalva-like maneuvers
  - Accompanied by nausea and/or vomiting

D) Not better accounted for by another International Classification of Headache Disorders, third edition (ICHD-3)

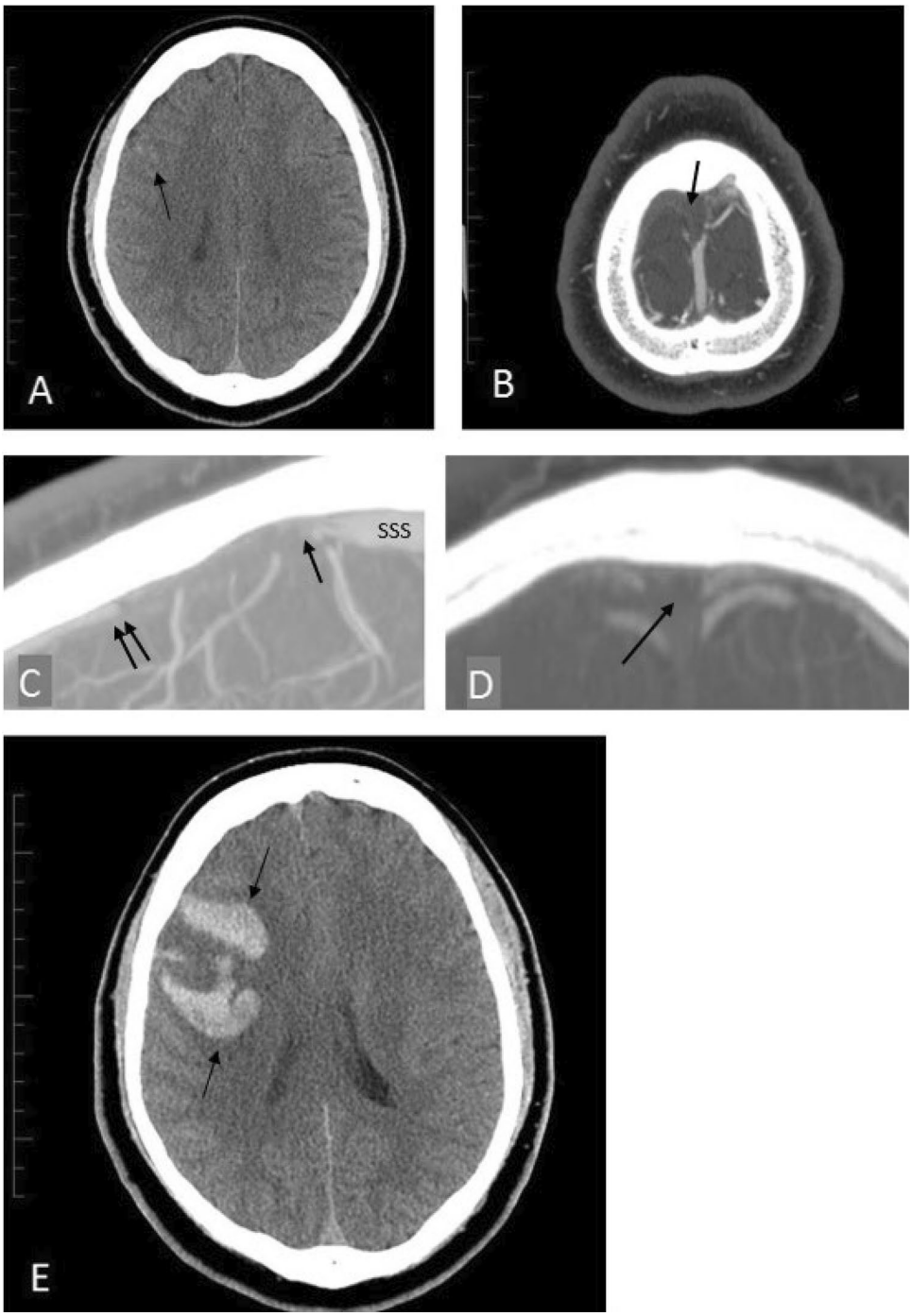


**Fig. 1** Sequential images from a patient with acute onset of superior sagittal sinus (SSS) thrombosis. 1a: Subtle subarachnoid and trace intraparenchymal hemorrhage (arrow) along the lateral convexity of the Right Frontal Lobe and located along the inferior frontal sulcus. 1b: Axial image of a CTA examination performed for evaluation of suspected infarct shows a filling defect (arrow) in the SSS, sinus thrombosis. This is further demonstrated on sagittal (1c) (double arrows anterior limit of thrombus, single arrow is posterior) and coronal (1d) MIP reconstructions of the CTA. Notice the large cortical draining veins that are not yet clotted, though likely distended due to venous hypertension. 1e: Progression of the SSS thrombosis to include resultant extensive multifocal intraparenchymal hemorrhage (arrows) in the Right Frontal Lobe

thrombus as a filling defect within the venous sinuses or veins. The presence of collateral venous channels suggests a compensatory response to venous outflow obstruction and supports the diagnosis of CVT. The sensitivity of CT for CVT can be time-dependent. The hyperdense sinus sign is more likely to be seen within the first week after thrombus formation. Dehydration, high hematocrit levels, or technical factors can lead to false-positive findings, while partial volume effects or the presence of dense pacchionian granulations can mimic or obscure the hyperdense sinus sign.

The treatment of cerebral sinus venous thrombosis (CSVT) is nuanced and requires a multifaceted approach. The mainstay of therapy is anticoagulation, which is recommended even in the presence of intracranial hemorrhage, a scenario that typically contraindicates its use in arterial strokes.

Intravenous UFH is usually first line for initial anticoagulation, particularly in patients with renal insufficiency or when rapid reversal may be required [42]. The dose is adjusted to maintain an activated partial thromboplastin time (aPTT) of 1.5 to 2.5 times the normal value. Low Molecular Weight Heparin (LMWH): Subcutaneous LMWH is preferred over UFH due to its ease of administration, better bioavailability, and lower risk of heparin-induced thrombocytopenia (HIT). Enoxaparin is commonly used at a dose of 1 mg/kg every 12 h or 1.5 mg/kg once daily. After initial treatment with heparin, patients are typically transitioned to oral anticoagulants. Vitamin K Antagonist warfarin is traditionally used, aiming for an INR of 2.0 to 3.0. The duration of therapy is generally 3 to 12 months, but it may be longer in patients with recurrent CSVT, ongoing risk factors, or thrombophilic disorders. Recent evidence suggests that DOACs such as rivaroxaban or dabigatran may be safe and effective alternatives to VKAs for the treatment of CSVT, although they are not yet universally recommended in guidelines, and their use is predominantly after the acute phase [43, 44].

If there is accompanying intracranial hypertension, acetazolamide may be used to reduce cerebrospinal fluid production. Corticosteroids use is controversial; they may be beneficial in cases with significant cerebral edema but are not routinely recommended. Repeated lumbar punctures may be performed to relieve pressure in cases of severe intracranial hypertension. In refractory cases, surgical options such as optic nerve sheath fenestration or ventriculoperitoneal shunting may be considered. Antiepileptic drugs are indicated if seizures occur. The prophylactic use of these drugs is not routinely recommended but may be considered in patients with cortical vein thrombosis or significant hemorrhagic infarcts. In patients with severe CSVT who fail medical therapy or present with rapid neurological deterioration, endovascular treatments such as mechanical thrombectomy or catheter-directed thrombolysis may be considered [43, 44]. These interventions are more invasive and carry a higher risk profile, so they are typically reserved for life-threatening cases. Adequate hydration, control of fever, and treatment of underlying conditions are important aspects of supportive care. Monitoring for and treating complications such as venous infarcts, hemorrhage, and hydrocephalus is also crucial.

### Headache from CNS Infections

Headaches arising from central nervous system (CNS) infections are typically a manifestation of meningeal irritation or increased intracranial pressure and can be a presenting symptom of various infectious processes, including meningitis, encephalitis, and brain abscesses [45].

The headache of meningitis is typically severe, diffuse, and rapidly progressive. It is often accompanied by nuchal rigidity, photophobia, and fever. Patients may also exhibit Kernig's and Brudzinski's signs [46]. The headache is thought to result from the inflammatory cytokines and increased intracranial pressure due to impaired CSF outflow. In bacterial meningitis, the onset is acute, while viral (aseptic) meningitis may have a more gradual onset. Headaches associated with encephalitis can be severe and are often accompanied by altered mental status, focal neurological deficits, seizures, and signs of systemic infection. Herpes simplex virus (HSV) is a common etiology, and prompt recognition is essential due to the availability of antiviral therapy [47]. The headache from a brain abscess is typically localized to the region of the abscess and may be associated with focal neurological deficits, fever, and signs of raised intracranial pressure. The character of the headache may change with posture and may worsen with Valsalva maneuvers.

A lumbar puncture (LP) is essential for diagnosing meningitis and encephalitis. CSF analysis typically shows pleocytosis, elevated protein, and, in bacterial infections, decreased glucose levels. PCR and cultures can identify specific pathogens. In acute bacterial meningitis, meningeal enhancement is often located along the cerebral convexity [48]. CT can diagnose brain abscess, and may also reveal hydrocephalus, cerebral edema or elevated intracranial pressure.

The treatment of headaches due to CNS infections is directed at the underlying cause. For bacterial meningitis, empiric broad-spectrum antibiotics should be started immediately after blood cultures and LP, without delaying for imaging if there are no signs of raised intracranial pressure or focal deficits. Treatment of viral meningitis is largely supportive. Empiric antiviral therapy with acyclovir should be initiated promptly while awaiting specific diagnostic testing. Surgical drainage may be necessary for brain abscesses, along with prolonged antibiotic therapy tailored to culture results.

### Headache from Obstructive Hydrocephalus

Hydrocephalus is a condition characterized by an abnormal buildup of cerebrospinal fluid (CSF) in the ventricles of the brain, which can lead to increased intracranial pressure. CSF normally circulates through the ventricles and over the surface of the brain and spinal cord, but in hydrocephalus, the fluid's flow is disrupted.

The blockage causing obstructive hydrocephalus can be congenital, stemming from genetic abnormalities or developmental disorders such as Neural Tube Defects, Aqueductal Stenosis, Dandy–Walker Syndrome, and Chiari Malformation. Acquired causes include brain hemorrhages, tumors, infections like meningitis, and post-inflammatory scarring that can obstruct CSF pathways [49]. Symptoms of hydrocephalus vary with age. In infants, it may

present as an unusually large head, a bulging fontanelle, vomiting, and irritability. Older children and adults may experience headaches, vision problems, balance issues, cognitive impairments, and incontinence. In older adults, normal pressure hydrocephalus can manifest with a triad of symptoms: gait disturbances, cognitive decline, and urinary incontinence [50].

The exact mechanism by which headache is caused in obstructive hydrocephalus is not fully understood. However, it is believed that the increased intracranial pressure caused by the accumulation of CSF in the brain ventricles leads to stretching and compression of pain-sensitive meninges and blood vessels, resulting in headaches. Rarely, it may be the result of excessive CSF production, which may be due to pathologies at the sites where CSF production takes place. The causes of (obstructive or non-communicating type) CSF increase are often due to cystic lesions, tumors, or obstructive membranes [51]. Interruption of CSF absorption can also cause hydrocephalus [50]. Obstructive hydrocephalus patients also known to have a long history of shunt revisions and refractory chronic headache.

The most common presenting symptoms of obstructive hydrocephalus is headache (100%), followed by vision-related symptoms (75%) [51]. Obstructive hydrocephalus is present in 70% to 90% of patients with posterior fossa brain tumors as diagnosis. However, only 20% to 30% of patients will require a means of long-term CSF diversion following tumor resection [51]. The mass effect caused by obstructive hydrocephalus may cause cognitive symptoms related to a decrease in the brain function [52•].

Treatment for hydrocephalus aims to alleviate the CSF buildup and address its underlying cause. Ventriculoperitoneal shunts [52•], which drain fluid into the abdominal cavity, are the most used. In some cases, an endoscopic third ventriculostomy (ETV) is performed, creating a bypass within the ventricular system to allow fluid to flow around the obstruction. Despite treatment, individuals with hydrocephalus may experience chronic headaches and require ongoing medical attention. Shunt systems can malfunction, necessitating revision surgeries. Hence, strategies that lead to normalization of CSF dynamics and reduce shunt dependency are valuable.

### Putting It All Together

While numerous conditions can result in a patient presenting with a headache, filtering out which secondary headaches is an art that requires a disciplined approach to the history and physical examination clues. There are several red and orange flags that should prompt the clinician to consider further workup and testing [53•, 54•, 55]. These are summarized in Table 2.

**Table 2** Headache: When to worry

| Headache feels different from any previous headache (pattern change) |
|---|
| Presence of focal neurologic deficits, neck stiff ness or altered mental status |
| Age > 50 years |
| Presence of systemic signs such as fever |
| History of HIV or autoimmune deficiency or neoplasm |
| Headache is progressive (getting worse) |
| Headache onset is abrupt |
| Pregnancy or puerperium |

## Conclusion

Headaches, while often benign, can occasionally be the harbinger of grave underlying pathologies. For the astute physician, the challenge lies not in diagnosing the common primary headache syndromes but in identifying those rare secondary headaches that portend significant morbidity or mortality. This overview elucidates some of the more sinister causes of headaches, emphasizing the importance of vigilance and a systematic approach in clinical evaluation.

**Author Contributions** LG, SCV, and TS wrote the main manuscript text and RR prepared figure 1 and tables. All authors reviewed the manuscript.

### Compliance with Ethical Standards

**Competing Interests** The authors declare no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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