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IMAGING (L MECHTLER, SECTION EDITOR)

Appropriate Use of Neuroimaging in Headache

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Abstract Headache may be caused by primary disorders, such as migraines, or secondary disorders, such as intracranial neoplasm or hemorrhage. Imaging plays an important role in differentiating between primary and secondary headache disorders. This article reviews the effectiveness of computed tomography (CT) and magnetic resonance imaging (MRI) in the evaluation of a patient with a headache. It also discusses the utility and cost-effectiveness of performing imaging studies in patients with a headache and a normal neurological exam. Emerging imaging techniques such as functional MRI, positron emission tomography (PET) scans, and voxel-based morphometry (VBM) are also discussed.

Keywords Headache · Neuroimaging · MRI · CT

Introduction

Headache is a common chief complaint in patients treated in the emergency department (ED) and can be related to a myriad of diagnoses. It comprises 1–3 % of all emergency room presentations and around 42 % of all neurology cases presenting to the ED [1–4]. It also accounts for 18 million of total outpatient visits in the USA each year [5•]. Although the majority of headache complaints derive from benign pathophysiology, it is important to note that some headaches can have much more serious underpinnings.

At present, headache disorders are generally classified as either primary or secondary disorders. Primary headaches are defined as headaches that are not caused by a specific medical condition, and include migraine, cluster headache, and tension headache. Secondary headaches are defined as headaches that are caused by a specific medical condition, and include stroke, brain tumors, and intracranial aneurysms. From an epidemiological standpoint, a review of patients presenting with headache and a normal neurological exam by Evans et al. revealed that the most common secondary causes of headache are strokes (1.2 %), brain tumors (0.8 %), hydrocephalus (0.3 %), arteriovenous malformations (0.2 %), subdural hematomas (0.2 %), and intracranial aneurysms (0.1 %) [6]. A table of common primary and secondary headache disorders is provided. [7, 8] (Table 1).

Obtaining a history and physical exam are the most important diagnostic steps for these patients. Although primary headache disorders make up the majority of headaches presenting to clinicians, it can be difficult to effectively identify a primary headache disorder from a secondary headache disorder without the presence of "red flags" in the history or an abnormal neurologic exam. Examples of red flags are as follows [9–19]:

- Neurologic symptoms or signs (e.g., altered mental status, weakness, diplopia, papilledema, focal neurologic deficits)
- Immunosuppression (HIV) or cancer
- Meningismus
- Onset of headache after age 50
- Headache triggered by exertion or Valsalva maneuver

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Table 1 Common primary and secondary headache disorders

Primary headaches	Secondary headaches
Migraine with or without aura	Acute post-traumatic headache
	Subarachnoid hemorrhage
Tension-type headache	Acute ischemic cerebrovascular disorder
Cluster headache	Unruptured vascular malformation
Paroxysmal hemicrania	Arteritis (e.g., temporal arteritis)
Idiopathic stabbing headache	Carotid or vertebral artery pain
	Benign intracranial hypertension (pseudotumor cerebri)
Cold-stimulus headache	
Benign cough headache	Intracranial infection
Benign exertional headache	Post-dural puncture headache
Headache associated with sexual activity	Medication-related headache
	Metabolic-disorder related headache
	Cranial neuralgias, nerve trunk pain and deafferentation pain

- Thunderclap headache (severe headache that peaks within a few seconds)
- Systemic symptoms (e.g., fever, weight loss, nuchal rigidity, scalp artery tenderness)
- Progressively worsening headache
- Red eye and halos around lights
- Head or neck injury
- Recent travel (foreign, domestic)

Although imaging studies can cause harm by exposing patients to potentially harmful radiation and increasing the cost of care, they can also exclude or identify high-risk pathology and help alleviate patient anxiety. From a research standpoint, emerging techniques such as functional magnetic resonance imaging (MRI), positron emission tomography (PET) scans, and voxel-based morphometry (VBM) can help us understand the pathophysiology behind certain headache disorders.

This review aims to suggest scenarios where neuroimaging should be considered in order to rule out a secondary cause of headache which could impact morbidity and mortality. This review also aims to provide a framework to recommend cases where neuroimaging may be omitted.

Imaging Modalities

Computed Tomography

Computed tomography (CT), also referred to as computerized axial tomography (CAT), is a common medical imaging technique that uses x-rays to generate high-resolution, three-dimensional imaging slices of a patient's anatomy. It is commonly the initial imaging study performed in the diagnostic work-up of patients who present with acute headache to the ED. The use of CT in the evaluation of medical conditions has increased significantly since the early 1990s and over 70 million CT studies are obtained in the USA each year. The demand for CT scans continues to increase on a yearly basis—recent studies have shown that the documented annual growth rate for CT utilization is 13 % [20•]. The increasing popularity of CT scans is likely due to a combination of reliability, accessibility, and the ability to quickly exclude life-threatening intracranial hemorrhage or bone abnormalities. Common indications for CT imaging in the ED include head trauma, disorientation, seizure, focal weakness, syncope, loss of consciousness, vertigo, and headache [15, 21].

In headache patients, CT scans are typically done without the use of intravenous contrast. However, if there is suspicion of an intracranial tumor, one may decide to use iodinated contrast. According to Rizk et al., in patients with acute non-traumatic headache, the majority of intracranial pathology seen on CT head can be identified without the addition of IV contrast [22].

Exposure to ionizing radiation is a disadvantage of CT [23]. The effective radiation dose for head CT is approximately 2–4 mSv depending if sequences are repeated with and without contrast [24]. One study showed that a third of projected cancers due to radiation from CT scan were from scans taken in adults between the ages of 35 and 54. The most common cancers included lung cancer, colon cancer, and leukemia [25]. In the pediatric population, it has been proposed that the cumulative ionizing radiation doses from 2–3 head CT scans in children age <15 could triple the risk of brain tumors and 5–10 scans could triple the risk of leukemia [26].

CT scans are costly, with an estimated cost per patient of US$340 for a CT brain scan [27]. Several studies have noted the low cost-effectiveness of CT imaging in patients with no abnormalities on neurological evaluation, citing that the cost of finding a case of brain tumor was estimated to be at least US$1265 for patients with abnormalities on neurological examination and US$11,901 for patients with normal findings on neurological examination [28–30].

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a common medical imaging technique that uses a strong magnetic field to generate high-resolution, three-dimensional imaging slices of a patient's anatomy. Unlike CT, MRI does not use ionizing radiation.

Although it is difficult to quantify the sensitivity of CT versus MRI in headache given the rapid development of both technologies, and increasing use of hardware and software algorithms to improve resolution and signal-to-noise ratios, MRI scans are generally capable of greater resolution and delineating soft tissue structures such as brain parenchyma.

Despite improved resolution of MRI techniques and lack of exposure to ionizing radiation, MRI scanners require patients to be fully enclosed in the magnet bore during an MRI scan, which complicates patient monitoring and can lead to claustrophobia. In the past, MR imaging required long examination times. Currently, with the help of high-speed technologies, MRI of the brain takes as little as 15–20 min. However, the lack of 24-h availability is still a problem at many institutions.

MRI scans are costly, with an estimated cost per patient of US$660 for an MRI brain scan [27]. As noted by several reviewers, given the effectiveness of CT scans at baseline, it is unclear if the identification of additional pathology on MRI studies would improve outcomes for headache patients with a normal neurological examination, because the proportion of abnormalities noted on CT scans that could potentially benefit from neurosurgical intervention is already small (as low as 0.01 %) [6, 8].

Secondary Headaches

As noted previously, although the majority of headaches do not reflect high-risk pathophysiology, some headaches can be symptomatic of conditions such as subarachnoid hemorrhage, intracranial neoplasm, carotid or vertebral dissection, or other conditions associated with significant morbidity and mortality. In patients over the age of 65, 15 % present with secondary headache disorders such as intracranial neoplasms, temporal arteritis, and strokes as opposed to 1–2 % in patients under age 65 [31•]. In this section, we discuss imaging considerations associated with the most common causes of secondary headaches.

Subarachnoid Hemorrhage

Patients presenting with subarachnoid hemorrhage often report a “thunderclap headache” that came on suddenly and is the “worst headache of their life.” In 80 % of non-traumatic cases, the most common cause is a ruptured intracranial aneurysm. The pattern noted on CT scan can suggest where the underlying aneurysm is located. CT is 91–98 % sensitive in the detection of subarachnoid hemorrhage within the first 12–24 h. After 12–24 h, the sensitivity decreases to 82–84 % and then decreases to 50 % in the following week [32]. It is important to note that the failure to obtain a head CT at admission accounts for 73 % of misdiagnoses [33••]. In patients with a demonstrated aneurysm on preliminary imaging studies, further imaging with conventional angiography, CT angiography, or MR angiography can be used to localize the aneurysm with a higher degree of precision. CT angiography and MR angiography have sensitivities greater than 85 % for aneurysms larger than 5 mm [5]. Around 20 % of cases of non-traumatic subarachnoid hemorrhage are due to a non-aneurysmal cause.

Other reasons to obtain a CT scan for a sudden onset headache include bleeding into a mass or arteriovenous malformation (AVM) and a mass or pituitary apoplexy. If the patient provides a history of head trauma, there should be suspicion for a subdural or epidural hemorrhage which can also be noted on CT.

Other Intracranial Hemorrhage

Other intracranial hemorrhages that may present with headache include subdural hematoma, epidural hematoma, and intraparenchymal hemorrhage. Subdural hematomas are often seen in the elderly and may be present after relatively minor head trauma that is acute or subacute. Conversely, epidural hematomas are more commonly caused by high-impact trauma causing damage to the middle meningeal artery. Intraparenchymal bleeding is commonly caused by a hypertensive etiology, but can also be related to hemorrhagic metastases, cerebral amyloid angiopathy, arteriovenous malformation, cavernous malformations, or coagulopathy. AVMs can present with intraparenchymal or subarachnoid bleeding. CT angiography (CTA), magnetic resonance angiography (MRA), or conventional cerebral angiography is needed to further characterize an underlying vascular malformation.

Suspected Intracranial Neoplasm or Metastasis

For suspected intracranial neoplasm or metastasis in patients with headaches and other neurological deficits, MRI of the brain with and without gadolinium is the study of choice. This is especially important in identifying posterior fossa tumors where this area is not well visualized by CT scan. The sensitivity and specificity for identifying an intracranial neoplasm with MR imaging are 92 and 99 %, respectively. In contrast, the sensitivity and specificity for identifying an intracranial neoplasm with CT are 81 and 92 %, respectively [5].

Carotid or Vertebral Dissection

Young patients presenting with sudden, severe, unilateral headache radiating into the neck raises suspicion for a dissection in the carotid or vertebral arteries, especially when associated with Horner syndrome. MRI brain with diffusion-weighted imaging is necessary to identify an acute stroke. MRA head without gadolinium and MRA neck with and without gadolinium including T1 fat-saturated axial images are used to localize the dissection along the carotid or vertebral arteries. Gadolinium is unnecessary in MRA head unless the patient has had a coiling or stenting procedure for aneurysm that could distort the image [33]. If there is contraindication to MRI, a CTA head and neck with contrast can be performed to identify the dissection. The sensitivity and specificity of MRI and CTA for the diagnosis of craniocervical dissection are similar at 83–99 %.

Giant Cell Arteritis

Giant cell arteritis is a common chronic vasculitis of medium- and large-sized arteries. New onset temporal headache in elderly patients should prompt a work-up for giant cell arteritis. A prospective multicenter trial provides evidence that MR imaging of the superficial cranial arteries can have a sensitivity of 83.3 % and specificity of 90.4 % [34]. Findings seen on MRI imaging of the superficial arteries include mural thickening causing narrowing of the diameter of the artery and wall enhancement showing vascular inflammation. Asymmetrical inflammation of the superficial arteries was a common trend in patients with temporal artery biopsy-proven GCA. These findings can fade after 5 days of systemic steroid therapy.

Meningitis/Encephalitis/Abscess

When meningitis is suspected, a CT brain is performed immediately to rule out cerebral edema so that a lumbar puncture can be performed without risk of herniation. MRI brain with and without gadolinium may highlight meningeal enhancement in the later stages of the disease but is unnecessary for the treatment of bacterial meningitis. In acute inflammatory lesions such as encephalitis, cerebritis, and tuberculosis, pathology appears hyperintense on DWI sequences. Brain abscesses also exhibit diffusion restriction and this pattern can be followed to monitor treatment response over time.

Idiopathic Intracranial Hypertension

In any patient with suspected increased intracranial pressure and headache, an MRI with and without gadolinium should be performed to rule out an intracranial mass or venous sinus thrombosis. Findings on MRI consistent with IIH include optic nerve head protrusion, posterior scleral flattening, increased orbital periorbital nerve CSF on T2 weighted, fat-saturated image, optic nerve enhancement on gadolinium enhanced sequences, an empty sella, cephaloceles, and transverse sinus stenosis [35].

Neuroimaging in Primary Headache Disorders

As noted previously, although some headaches can reflect high-risk pathophysiology, the majority of patients with headache are not at risk for high morbidity or mortality, especially if they do not exhibit any focal neurological deficits. In this section, we discuss imaging considerations associated with the most common causes of primary headaches.

Migraine

According to the Internal Classfication of Headache Disorders, third edition (ICHD-3) beta, migraine is a recurrent headache disorder manifesting in attacks lasting 4–72 h. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. It is further divided based on headache frequency, into episodic migraine, 15 headache days monthly and chronic migraine 15 headache days a month for at least 3 months. In patients who have their typical episodic migraine with a usual frequency and normal neurological exam, neuroimaging is typically unnecessary. This was suggested by a meta-analysis of studies which showed abnormalities were found in 0.18 % of patients [21].

A recent meta-analysis performed by Bashir et al. indicated that migraine is a risk factor for white matter abnormalities, infarct-like lesions (especially in the posterior circulation), and volumetric changes in the gray and white matter [36]. MRI brain without gadolinium often detects white matter hyperintensities (WMH) on fast-recovery, fast-spin echo T2 and fluid-attenuated inversion recovery sequences especially in patients with aura. These lesions are typically silent and nonspecific. A recent study examined these nonspecific lesions over time and showed a correlation between migraine aura duration and the number of new WMH over a follow-up period of 33 months. There was also a correlation between the number of migraine attacks with aura each year and the number of new WMH over 33 months [37].

The ARIC MRI study, a prospective cohort study published in *Neurology* studied WMH in patients with migraine without aura and patients without any headache. After looking at data between 10 years, they found that migraine patients without aura had an 87 % greater chance of having a greater WMH score than those without headache cross-sectionally [38]. They did, however, show that these WMH progressed over time. WMH in migraine commonly involves the frontal lobes [39].

Functional imaging studies have provided insight into the pathophysiology of migraine. Using d positron emission tomography scans, Maniyar et al. triggered the premonitory phase followed by migraine with glyceryl trinitrate. In turn, specific areas were activated during a migraine attack—the posterior hypothalamus, midbrain tegmentum, periaqueductal gray, dorsal pons, and several regions of cortex. The authors suggest that activation of these areas, especially the hypothalamus, may explain why migraines are triggered by changes in homeostasis [40].

Diffusion tensor imaging has been performed during migraine attacks and supported previous findings of brainstem involvement in migraine. DTI has shown increased ADC values in red nuclei during migraine attacks [41].

Due to previous studies showing thalamic activation in migraine attacks, another functional study using 3D MRI showed significant volume reductions of the anterior thalamic nucleus, central nucleus, lateral dorsal nucleus, and lateral posterior thalamus in migraine patients compared to controls [42]. Imaging studies not only contribute to the work-up of migraine, especially when ruling out a secondary headache disorder, but also contribute to the understanding of pathophysiology.

Tension Headache

According to the ICHD-3 beta, a tension headache is typically bilateral, pressing or tightening in quality, and of mild to moderate intensity, lasting minutes to days [43]. Tension-type headache is the most prevalent primary headache disorder in the world with lifetime prevalence up to 78 % [44]. The pain does not worsen with routine physical activity and is not associated with nausea, but photophobia or phonophobia may be present. Patients with tension headache should get an MRI brain once to rule out an underlying brain tumor. Intracranial neoplasms more commonly present with a tension type headache phenotype than a migraine headache phenotype [44].

Cluster Headache

The ICHD-3 describes cluster headache as attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal, or in any combinations of these sites, lasting 15–180 min and occurring once every other day to eight times a day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, and ptosis and/or eyelid edema, and/or with restlessness or agitation [43]. The condition is predominant in men and age of onset is usually between 20–40 years. Cluster headache is also unique due to its circadian and circannual periodicity. The attacks occur at a stereotyped time of the day or evening, usually during the night. Several studies have pointed to hypothalamic dysfunction as the basis for cluster headache pathophysiology which may explain its circannual and circadian periodicity. Cluster headache is the most common trigeminal autonomic cephalgia (TAC) and affects <1 % of the population.

Functional imaging studies using positron emission tomography (PET) scans in a large patient sample have shown ipsilateral hypothalamic gray matter activation during an acute attack. A voxel-based morphometric MRI study showed higher density in the same area [45]. This finding has paved the way for deep brain stimulation in the posterior hypothalamus gray matter for patients with medically intractable cluster headache [46•]. Hypothalamic involvement has been shown in the other TACs such as short-lasting neuralgiform pain with conjunctival injection and tearing (SUNCT), paroxysmal hemicrania and hemicrania continua. This suggests that the TACs have a common pathophysiology. In contrast to migraine headache, there is no brain stem activation during acute cluster headache episodes.

An MRI brain should be considered on the initial diagnosis of cluster headache to exclude a mass, vascular lesion, or other midline lesions which have been reported in the literature. Secondary causes for cluster headache include vascular causes in 38 %, tumor in 25.7 %, and inflammatory/infectious in 13.5 % [47]. A CT may be obtained in the urgent setting if an MRI is not immediately available.

Conclusion

As seen in this review article, there is a robust role for neuroimaging in the diagnosis and characterization of headache-causing pathophysiology. While CT and MRI scans allow one to diagnose certain pathological conditions, their relative utility is significantly decreased in patients with chronic headache and no focal neurological signs. New techniques, such as PET scans and fMRI have helped us understand the mechanisms behind primary headache disorders, and have led to advances in surgical treatment. With advances in computational power, we anticipate that techniques such as voxel-based morphometry will yield a better understanding how to treat and manage headaches.

Compliance with Ethics Guidelines

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