

Review

Headache Disorders: Differentiating Primary and Secondary EtiologiesJairo Hernandez^{1,*}, Eduardo Molina¹, Ashley Rodriguez¹, Samuel Woodford¹,
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Abstract

In the initial assessment of a headache patient, several dangerous secondary etiologies must be considered. A thorough history and physical examination, along with a comprehensive differential diagnosis may alert a physician to the diagnosis of a secondary headache particularly when it is accompanied by certain clinical features. Evaluation and workup include a complete neurological examination, consideration of neuroimaging, and serum/spinal fluid analysis if indicated. Careful attention to the patients' history and physical examination will guide the diagnostic work-up and management. In this review, we summarize the diagnostic workup of various primary and secondary headache etiologies. Although most headaches are primary in nature, it is essential to screen for headache "red flags", as they can suggest life threatening secondary etiologies. When secondary causes are suspected, appropriate neuroimaging can further differentiate the underlying cause. The appropriate imaging is dependent on the most likely secondary etiology, which is deduced from history and physical examination. When no red flags are present, primary headaches are more likely. These can be differentiated by frequency, location, duration, triggers, and presence of aura. The different clinical presentations for secondary headaches, as well as the distinguishing features for primary headaches are outlined in this review.

Keywords: headache; subarachnoid hemorrhage; migraine; tension headache; cluster headache**1. Introduction**

Headaches are one of the most common disorders of the nervous system and one of the largest contributors to disability [1]. Although most headaches in the emergency department (ED) are benign, the fatal potential of most secondary forms of headache makes it imperative to consider and rule out secondary etiologies [2]. Headache disorders are divided into primary and secondary headaches. Primary headaches represent idiopathic pain conditions, while secondary headaches arise from serious underlying pathology and are associated with high morbidity and mortality. Headache diagnosis is made following careful collection of the clinical history and physical examination, to identify "red flags" of secondary headaches and intervene expeditiously or initiate conservative treatment of primary headaches [3,4].

2. Initial Evaluation

Patients presenting with headaches need to be screened for primary vs secondary etiologies. Optimal diagnostic strategies to identify headaches requiring immediate intervention include historical information, physical examination findings, demographic data, social history, and family history [3]. Collection of the patient's history should therefore include questions characterizing the pain and associated symptoms. Critical questions include the location, time of onset and progression of pain, aggravating and alleviating factors, intensity, history of recent head trauma or

prior headaches, and associated symptoms (nausea, vomiting, photophobia, etc.). "Red flags" associated with secondary headaches (Table 1, Ref. [5]) are crucial to identify [2]. Physical examination should be completed with careful assessment of clues obtained during the history. It should include blood pressure measurements, assessment of mental status, and cranial nerve (CN) examination including but not limited to fundoscopic examination, gait, and facial strength. An anomalous gait may manifest in the setting of CN dysfunction, in particular the optic nerve. This subtle observation could steer the diagnostician to CN disorders. If an infection is considered, the temperature should be measured [6]. Medications should also be evaluated for medication overuse-induced headaches. Although most individuals are affected by primary headaches, the first mandatory step in the examination is the exclusion of secondary forms, considering the high risk to the patient's life in most of them [2].

3. Secondary Headaches**3.1 Subarachnoid Hemorrhage**

Subarachnoid hemorrhage (SAH) is a life-threatening medical emergency that classically presents within the emergency department and characterized by a thunderclap headache, defined as a severe headache with an acute onset that reaches maximum intensity in less than one minute [7]. Patients usually describe the event as "the worst headache of my life" [8]. Nevertheless, the headache in-



Table 1. An overview of the mnemonic SNNOOP10 that considers the “red flag” features that may suggest an underlying secondary etiology for acute or subacute headaches.

Worrisome “red flag” features of secondary headaches, SNNOOP10	
Clinical characteristic	Other conditions to rule out
S Systemic symptoms, including a fever	Non-vascular intracranial events from an inflammatory or infectious process
N Neoplasm history	Brain neoplasm or metastasis
N Neurologic focal deficits (e.g., diminished level of consciousness)	Vascular intracranial or cervical events; brain abscess; meningitis; opportunistic infections
O Onset is sudden	Subarachnoid hemorrhage and other secondary headaches with vascular etiology
O Older age (50+ years)	Giant cell arteritis or other vascular intracranial process; neoplasms and other non-vascular intracranial disorder
P Pattern of headache changes	Neoplasm, headaches attributed to intracranial or cervical vascular and non-vascular etiologies
P Positional headache in nature	Intracranial hypertension or hypotension
P Precipitating factors include sneezing, coughing, or exercise	Posterior fossa malformations; Chiari malformation
P Pregnancy or puerperium	Acute intracranial or cervical vascular etiologies
P Painful eye with autonomic features	Pathology in posterior fossa, cavernous sinus, or pituitary gland; ophthalmic etiologies
P Post-traumatic onset of headache	Headaches related to intracranial or cervical vascular etiologies; post-dural puncture headaches; headaches related to pre-eclampsia; venous sinus thrombosis; anemia; hyperthyroidism; hypothyroidism; diabetes
P Pathology of the immune system (e.g., HIV, T-cell lymphoma)	Headaches related to intracranial non-vascular events; brain abscess; opportunistic infections
P Painkiller (analgesic) overuse headache, or new drug at onset of headache	Headaches related to non-vascular intracranial etiology related to adverse drug metabolite interaction

tensity can vary, making the key symptom an abrupt-onset headache. The presence of acute-onset headaches should prompt at least a consideration of SAH [9]. In addition to an acute headache, SAH often presents with other neurological symptoms including cranial neuropathies, focal weakness, altered level of consciousness, and meningism. In patients who have positive neurological symptoms, the diagnosis is straightforward as an abnormal neurological exam prompts immediate imaging. Unfortunately, in patients whose only presenting symptom is a headache, studies have reported the frequency of misdiagnosis ranging from 12 to 51% [10–13].

While a thunderclap headache should always prompt a workup, since a wide range of other etiologies can present with a thunderclap headache, additional clues in the clinical history can help narrow the differential diagnosis [14]. A prospective observational study evaluated the clinical characteristics of the presenting headache in people presenting to the emergency department with SAH. In the cohort of 158 patients, 20 patients had SAH, and 138 patients did not. Distinguishing features included headache in occipital location, no presence of prior headache, “stabbing” quality and meningismus.

Even with these distinguishing features, it can be difficult to determine which patients warrant further investi-

gation for SAH. The most studied decision-making tool is the Ottawa SAH rule which has been prospectively validated [15]. The rule determined further investigation for SAH is needed if one or more of the following six risk factors are met: Any patient of age 40 years or older, presence of neck pain or stiffness, onset during exertion, a thunderclap headache, witnessed loss of consciousness, and limited neck flexion on examination [16]. The Ottawa SAH Rule had a 100% sensitivity, 13.6–15.3% specificity, and similar neuroimaging rates in subsequent validation studies [17]. While it is a great rule-out test with 100% sensitivity, the low specificity means it is unlikely to reduce the number of unnecessary imaging studies.

When clinical suspicion for SAH has been established, non-contrast computed tomography (CT) is the first diagnostic tool (Fig. 1, Ref. [18]). A meta-analysis in 2016 showed that a non-contrast CT completed within six hours of headache onset had a 98.7% sensitivity, with many considering a negative head CT within this timeframe to be a “rule-out” for SAH [19]. If non-contrast CT is not definitive, the next recommended tool is a lumbar puncture (LP). Two elements in LP raise concern for SAH: red blood cells (RBCs) and xanthochromia (bilirubin in cerebrospinal fluid). Given the sensitivity of a CT performed within 6 hours, patients should be made aware of the low diagnostic

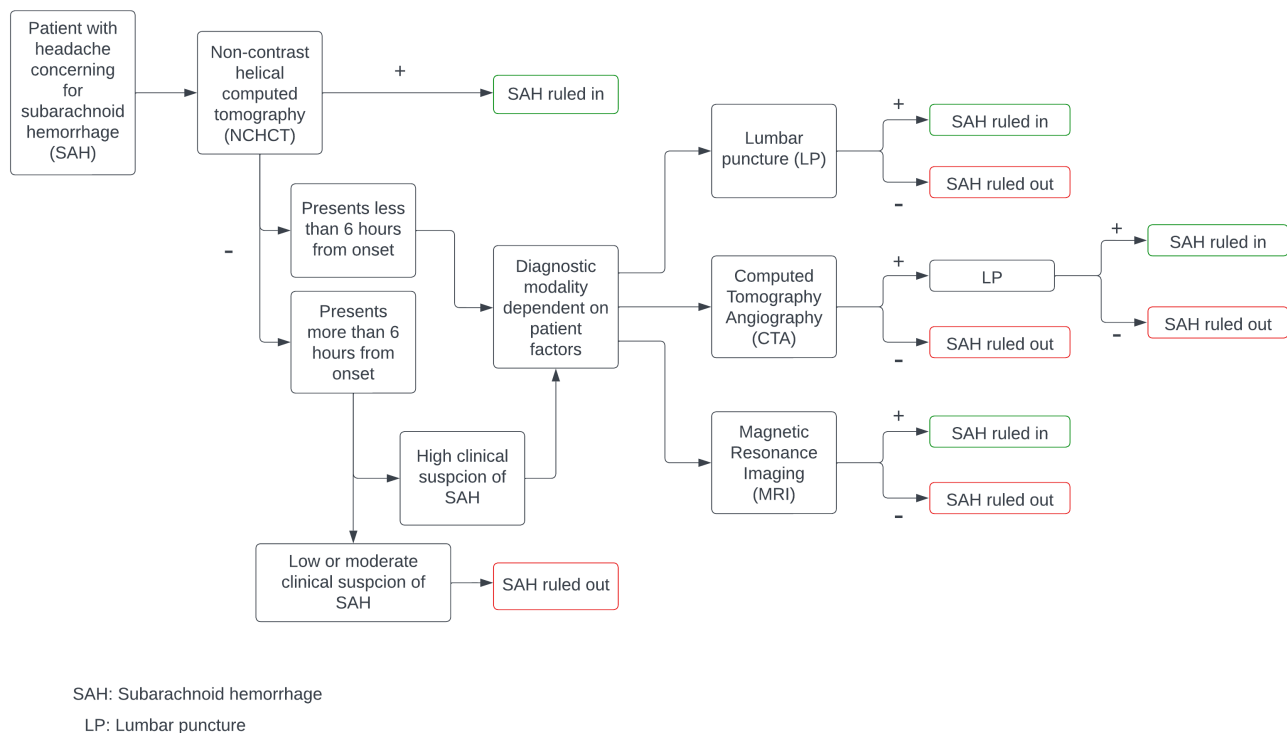


Fig. 1. Diagnostic algorithm for patients with sudden onset severe headache concerning for subarachnoid hemorrhage (SAH) [18].

utility of an LP in this setting [20]. If the imaging is completed after the six-hour timeframe, the sensitivity of CT drops to 85.7%, increasing the diagnostic utility of LP as the probability of SAH after negative CT also increases [21]. Non-contrast CT followed, if negative, by LP is the current diagnostic algorithm supported by the literature [22].

3.2 Subdural Hematoma

In the context of subdural hematoma (SDH), headache is the primary symptom that manifests reported at rates of up to 77% [23]. The symptoms of SDH include generalized symptoms including headache, seizure, and deficits in memory. It is often characterized by a history involving head trauma, though may be secondary to iatrogenic causes such as lumbar punctures. In the latter, this should be included in the differential if the context of the described symptoms and specific procedural history.

The gold standard for diagnosis is in the form of imaging, namely CT. Visual observations range in the form of hyperdense lesions. Supportive measures towards diagnosis also include complete blood count (CBC), particularly in the form of hemoglobin and hematocrit level which can occasionally display bleeding, although most patients present with normal CBC [24]. Other lab analyses include a basic metabolic panel (BMP) of which hyperkalemia secondary to red blood cell lysis may likewise indicate significant bleeding, although this is not necessary for a diagnosis [24].

The preferred treatment modality is surgery which may vary in the form access including endoscopically or through a more traditional craniotomy. Less invasive outlets may be suitable depending on the patient profile. For example, those currently receiving antiplatelet drugs may be treated following withdrawal of such, given that the hematoma is small enough to respond to this. Other aspects of the hematoma should also be addressed such as seizure prophylaxis, though this should abide by certain indications in mind. This has included notable associations between lower Glasgow Coma Scale (GCS) scores on presentation and increased risk of seizures [25].

3.3 Acute Bacterial Meningitis

Acute bacterial meningitis (ABM) is a disease with acute onset and high rates of morbidity and mortality [26]. Community-acquired bacterial meningitis is predominantly caused by three pathogens: *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B. Specific groups, including neonates, pregnant women, and transplant recipients are especially susceptible to ABM from *Listeria monocytogenes*, *Escherichia coli*, and Group B *Streptococci* [27]. Early recognition and initiation of antimicrobials is essential to minimize death and complications of ABM.

Although history and physical exams alone cannot confirm the diagnosis of meningitis, they can establish strong clinical suspicion. In one prospective study of 696

Dutch patients with community-acquired ABM, 95% of patients had at least two of the following symptoms: neck stiffness, headache, fever, and altered consciousness [28]. After suspicion has been established, LP is the key investigation to confirm the diagnosis and establish the cause of infection (Table 2, Ref. [29]). Classic cerebrospinal fluid (CSF) findings for ABM include raised opening pressure, neutrophil-predominant pleocytosis, elevated protein (above 100 mg/dL), and reduced CSF glucose (often below 30 mg/dL) [29,30]. CSF pleocytosis is suggestive of meningeal inflammation, of which infection is the most common cause. Van de Beek *et al.* [28] reported that >90% of patients presenting with ABM had a CSF leukocyte count >100 cells/ μ L. Once a strong clinical suspicion of bacterial meningitis is established, empirical antimicrobial therapy should be initiated. The choice of initial therapy is based on the most common bacteria causing the infection according to the clinical setting, patient's age, and immunocompromised state [31].

Once empiric treatment is started, it is necessary to obtain the *in vitro* susceptibility of the causative pathogen and rationalize treatment. Cerebrospinal fluid culture is the “gold standard” for diagnosis, while CSF gram staining, polymerase chain reaction (PCR), and latex agglutination testing are additional tools that can aid patients with negative CSF cultures. Of note, CSF sterilization can occur within 2–4 hours after antibiotic administration, so LP should be performed as soon as possible to maximize pathogen identification through CSF culture [31].

3.4 Viral Associated Headache and Meningitis

Though the previous section described the manifestation of headache in the setting of bacterial meningitis, aseptic meningitis is an alternative cause for headaches, with viral meningitis being the most prevalent form. It can be caused by an array of viruses though genus enterovirus has been noted to be the most frequent cause in multiple areas globally [32]. Its specific pathophysiology involves viral spread towards the meninges of the brain homogeneously, via nerve endings, or reactivation from a latent state within the nervous system [33].

Likewise, to bacterial meningitis, there are few distinguishing factors which may definitively build a diagnosis. Though, symptomatically, this can occur as a fever, headache, photophobia, nuchal rigidity, among other symptoms [32]. Unfortunately, the generalizability of certain symptoms such as headache and fever only provide mild and initial suspicion for viral meningitis. Though these symptoms in concordance with nuchal rigidity and photophobia may build a stronger diagnostic profile. Other key details within the aspect of the history if whether the suspected patient has traveled to a region particularly prevalent for responsible viruses [34]. More direct measures of evaluation include lumbar punctures or PCR tests if indicated by neurological deficits, and other neurologic symptoms such

as seizures. The former may reveal mononuclear pleocytosis, and the latter presence of specific viruses [35]. A considerable issue in diagnosis is the distinction between viral and bacterial meningitis as this may tailor the treatment algorithm. Regarding viral meningitis, a rule-out approach is adopted by looking for bacterial specific biomarkers, such as positive gram stains, CSF protein count over 80 mg/dL, and neutrophil count greater than 10,000 cells/mm³ [32].

As with many viral pathologies, supportive care remains the mainstay of treatment for viral meningitis. This may be in the form of fluid and electrolyte replacement and pain management [33]. An important decision in practice, however, is the decision often to begin empiric antibiotic therapy prior to ruling out bacterial meningitis [36].

Lastly, viral associated headaches in the absence of cranial localization, such as meningitis, are a prevalent cause of headaches. This is a particularly salient point in a post COVID-19 era. While it is true that viral infection may progress to meningitis, thereby manifesting as a headache, a more prevalent mechanism involves a form of systemic inflammation. Other symptoms that may arise include a fever, fatigue, cough, dyspnea, diarrhea, and especially so in the context of COVID-19, a loss of taste and smell [37]. In a recent study by Straburzyński *et al.* [37], 130 patients were assessed for symptomatic presentation following COVID-19 diagnosis. Headache was reported as the most prevalent symptom at a rate of 72%, among other symptoms. These included facial pain, cough, fever, and shortness of breath. To note, the unspecific nature of these symptoms creates significant reliance on other modalities of diagnosis including antibody, antigen, or gene detection with the latter being the most utilized, via Reverse Transcription Polymerase Chain Reaction (RT-PCR).

Treatment for COVID-19 has gained considerable traction due to the urgency of its inception. This has included both supportive therapies as with the majority of common viral afflictions. COVID-19 specific therapies have evolved in the form of antiviral therapies such as Molnupiravir, Paxlovid, and Remdesivir. Supportive therapy particularly emphasizes oxygenation treatment in the form of nasal cannula, nonrebreather, or Venturi mask depending on severity [38].

3.5 Giant Cell Arteritis

Giant cell arteritis (GCA) is a vasculitis that predominantly affects medium and large-sized arteries in individuals older than 50 years. With an increasingly aging population, GCA is predicted to become a significant health issue in the coming decades [39]. The symptoms of GCA can be classified into four subsets: systemic symptoms, cranial arteritis, extracranial arteritis, and polymyalgia rheumatica (PMR). Typically, the disease manifests with a temporal headache as the most common symptom, and jaw claudication as the most specific manifestation [40,41]. Scalp tenderness and visual disturbances can also be present.

The diagnosis of GCA is made primarily on clinical presentation and is supported by laboratory evidence of an acute phase reaction (such as elevated erythrocyte sedimentation rate). On physical examination, temporal arteries may be thickened or tender on palpation, and pulses may be diminished or absent. Cerebrovascular accidents (transient ischemic attacks or strokes) can be present in 3–7% of cases, and blindness can occur in 15–20% of patients due to severe cranial ischemic events [42,43]. Given the severity of events that may occur at disease onset, GCA is considered a medical emergency. Patients with a suspected diagnosis of GCA should be referred to a specialist, but treatment with glucocorticoids should not be delayed by diagnostic procedures such as temporal artery biopsy or imaging [44].

3.6 Central Nervous System Tumors

Headaches may rarely be indicative of a developing tumor [45]. Although headaches representing tumors are uncommon, 50%–60% of brain tumors present with headaches [46]. When evaluating 111 patients with brain tumors, 17% reported severe morning headaches. Additionally, 45% of those participating in the study stated the headache was the worst symptom endured [47]. Tumors typically cause the sensation of pain by displacing structures or available spaces within the brain. This congestion of anatomical regions causes specific points of compression that elicit headache responses [48]. The cardinal regions include traction on the veins draining into the large venous sinuses, traction on major arteries within the base of the brain, tumor pressure on cranial nerves with pain afferent fibers from the head, and distention-dilation of the intra/extra-cranial arteries [49].

Patients diagnosed with malignant gliomas experienced headaches generally 50–60% of the time, however, it was the only symptom 2% of the time [50]. Other symptoms that accompany headaches include epilepsy and blurred vision [51]. The headache is described as nonspecific and dull [52]. Individuals with malignant gliomas may display aberrant cognitive behaviors—falsely indicating dementia or psychiatric disorders. Among others, the patient can present with hemiparesis, visual disturbances, language difficulties and seizures [50].

Meningiomas generally consist of slow developing intracranial tumors. Headaches are a frequent symptom of meningiomas representing roughly 67% of patients. Often diagnosed incidentally, meningiomas are benign in 90% of instances [53]. Since the majority of meningiomas are frequently asymptomatic, a reliable diagnosis must be conducted radiologically. Although seizures and headaches may accompany meningiomas, the manifestation is unreliable and without diagnostic precision [54].

Pituitary adenomas are mostly benign, slow-growing tumors that associate to the anterior pituitary gland. Because pituitary adenomas are benign, the majority are dis-

covered incidentally [55]. Typically described by size and origin, pituitary adenomas can be described as microadenoma or macroadenoma. Certain pituitary adenomas are functional and create an influx of pituitary specific hormones. Other growths are nonfunctional; however, continual expansion may compress surrounding neural structures [14]. Common symptoms include but are not limited to visual impairment (40–60% of patients) due to optic chiasm compression, headaches, and hormonal deficiencies from the active growths [56,57].

3.7 Acute Ischemic Event

When considering blood flow cessation, acute cerebral ischemia is frequently associated with headaches [58]. Specifically, more than 25% of cerebral ischemic events are associated with headaches [59]. Cerebral ischemia is commonly caused by atherosclerotic disease manifesting in the carotid and vertebrobasilar circulations [60]. If untreated, neuronal tissue may become damaged, form lesions, or die [61]. In addition to headaches, cerebral ischemia can be identified by loss of balance, reported visual disturbances, facial weakness or asymmetry, extremity weakness, and difficulty speaking [62]. To achieve a precise diagnosis, a computed tomography (CT) scan is utilized to visualize reduced blood perfusion [63].

In addition, cervical arterial dissection (CeAD) is a type of stroke that is prevalent in younger populations. Regarding presentation, it is common for patients to suffer from ischemia, but not yet dissection [64]. Although the exact etiology is difficult to assess, the presentation can be accompanied by cerebral ischemia, cervical or cranial pain, Horner's syndrome and cranial nerve palsy [65]. Symptoms should be further investigated with CT angiography. If CT evaluation validates a CeAD diagnosis, long-tapered arterial stenosis or occlusion, dissecting aneurysm, intimal flap, double lumen, or intramural hematoma may be present [66].

3.8 Idiopathic Intracranial Hypertension

Idiopathic hypertension (IIH) refers to an increase of intracranial pressure without a direct causal link [67]. IIH exists in a larger category known as pseudotumor cerebri syndrome (PTCS). Primarily, IIH can manifest into headaches, vision loss, and pulsatile tinnitus. If intervention is prolonged, a decremented life quality and/or loss of vision are frequent outcomes [68]. IIH is diagnosed according to the ICHD-III criteria [69]. When observing the ICHD-III criteria, a new headache with significant worsening of a pre-existing headache, accompanied by a CSF pressure ≥ 250 mm—in addition to pulsatile tinnitus and papilledema, may warrant a primary IIH diagnosis—assuming a plausible ICHD-3 diagnosis is unavailable [70]. However, if the ICHD-III criteria is fulfilled and a known cause is discovered, it will be diagnosed as a secondary PTCS [67].

When investigating diagnostic specifics, papilledema may be detected on ophthalmologic examination. In addition to this, a full neurologic exam should reveal no deficits, barring cranial nerve (CN) abnormalities, namely CN VI. Magnetic resonance imaging (MRI) or CT for venography should be ordered to rule out cranial structural abnormalities—these include, but are not limited to the absence of hydrocephalus, anomalous masses, lesions, and parenchyma. Recently, there has been growing recognition of the utility of imaging in the diagnosis of IIH. MRI of IIH patients can reveal a variety of findings including posterior scleral flattening, empty sella, cerebellar tonsillar herniation, transverse venous sinus stenosis, and optic nerve sheath distension [71]. Patients with opening pressures below the cutoff can now be considered for a diagnosis of IIH if they exhibit symptoms and radiologic sign [72]. A recent retrospective analysis of over 200 demonstrated that MRI exhibited a sensitivity of 74.8% and specificity of 94.7% for IIH [71].

Lastly, a lumbar puncture is required to assess two features of the cerebrospinal fluid. (1) The composition of the CSF should be normal. (2) Opening pressure (OP) is greater than 250 mm in adults and 280 in children, precluding exceptions such as obesity and improper execution of the LP (lateral decubitus position) [61]. A notable stipulation regarding the opening pressure is that physiological variation between individuals creates a “grey zone” for OP. That is, between 250–300 mm, for some this may be either physiological or pathological. Therefore, the clinical utility of the CSF OP is exceedingly reliant on other portions of the diagnostic workup, such as the history.

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3.9 Intracranial Hypotension

Spontaneous intracranial hypotension (SIH) is characterized by an incapacitating orthostatic headache syndrome caused by CSF leakage and the resulting diminished pressure of the subarachnoid space. CSF leakage can occur secondary to CSF-venous fistula, dural breach, or a leaking meningeal diverticulum. A recent study found the incidence of SIH for all ages was 3.7 per 100,000 [73]. In a recent meta-analysis of 1694 SIH patients, headache was present in 97% of these patients, with most of them experiencing orthostatic headaches [74]. Classically, the headache worsens with an upright posture and is alleviated within 15–30 minutes of lying in a recumbent position [75]. Common associated symptoms include visual symptoms (photophobia, visual loss, diplopia), cognitive impair-

ment, back pain, reduced level of consciousness, movement disorders (poor balance, ataxia, gait disorder, tremor), and ear-related symptoms (vertigo, hyperacusis) [74].

Since only about half of patients with SIH present with diminished opening pressures, imaging emerges as a key aspect of diagnosis [76]. A head MRI is the mainstay initial imaging modality for SIH, as it can detect signs of CSF volume depletion, like descent of the brainstem, diencephalon, mesencephalon, and cerebellar tonsils. Other signs include flattening of the anterior pons, optic chiasm, crowding of the posterior fossa, and obliteration of basal cisterns [77]. Certain MRI measurements have been described for a more qualitative assessment of CSF hypovolemia, these include suprasellar cistern distance, pontomesencephalic angle, venous-hinge angle, mamillopontine distance, tonsillar herniation length, pituitary height, and area cavum veli interpositi. Nonetheless, none of these findings can be considered specific for SIH, but rather the constellation of MRI and clinical findings can suggest a patient has this condition [78]. Most cases of SIH respond to non-targeted epidural blood patches, and patients that do not respond can be further worked-up with myelography to localize the leak and address it with transvenous embolization, targeted patching, or surgery [74].

3.10 Unruptured Vascular Malformations

Unruptured brain arteriovenous malformations (bAVMs) involve a direct connection between the artery and vein in the brain (due to a lack of a capillary bed), a pathologic complex known as the nidus. The nidus creates arteriovenous shunting producing an aberrant form of venous drainage [14]. The etiology of this poor vessel formation itself may be attributable to both inherited and sporadic, malformative angiogenic development within the brain; though, approximately only 5% of cases are thought to be related to genetic syndromes (hereditary hemorrhagic telangiectasia [HHT]) [79]. Clinical presentation includes migraine-like headaches in 14% of patients (with or without an aura), typically localized to the occipital region, seizures, hemiparesis, and visual disturbances [80,81]. Fifteen percent of patients will remain asymptomatic until the onset of a presenting event. Though less ideal, greater than 50% of this population will acutely display the aforementioned symptoms requiring urgent care secondary to an intracranial hemorrhage. Additionally, although rarely the direct cause of headaches, bAVMs are often an important diagnostic feature found when evaluating headaches [14].

Diagnosis of a bAVM also relies heavily on imaging modalities. CT is very sensitive in detecting hemorrhage in light of new neurological deficits, namely CT angiography, raising suspicion for bAVM [79]. Following, digital subtraction angiography (DSA), the gold standard for diagnosis of bAVM, is implemented [82]. While CT angiography or

MR angiography may be sufficient, they lack real-time detection disallowing hemodynamic characterization, among other risk assessments. This makes DSA superior, and significantly encouraged over other imaging tools. Anomalous considerations include the fact that bAVMs secondary to HHT is very small (<1 cm) and should utilize post-contrast enhanced imaging [79].

Additionally, cerebral venous thrombosis (CVS) entails a dysfunction of prothrombotic and thrombolytic processes—forcing venous blood back into small vessels and capillaries [83]. Regarding patient phenotypes, CVS manifests commonly in young adults, women of child-bearing age, and children. The symptomatic presentation consists of headaches, seizures, distorted consciousness, and neurological focal indicators. Symptoms may present as singular or multiple [84]. To appropriately diagnose CVS and exclude other disorders, radiological investigations must take place [85].

3.11 Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) is a disruption of the homeostatic response to cerebrovascular blood flow. The sequela to disease affliction involves (1) autoregulated responses in cerebral blood flow to generalized fluctuations in blood pressure, (2) rapid systemic hypertension, (3) inability of response to compensate resulting in hyperperfusion, (4) cerebral vessel damage, atypical protein extravasation, and vasogenic edema [86]. Symptom presentation mainly includes a “dull” headache in 50% of patients, generalized tonic-clonic seizures in 81% of patients [87], visual disturbances, encephalopathy [88], and lastly focal neurological deficits [88]. Despite an overwhelming penchant to manifest in a generalized fashion, status epilepticus and complex-partial seizures may also be observed [89]. In a similar vein, within a smaller subset of patients, the headache may be felt and described more so as a “thunderclap” headache. Visual disturbances exist in the form of blurred vision, diplopia, and cortical blindness [90]. And again, is important to be sensitive to the patient demographic as this may affect the diagnostic value of specific symptoms. For example, a prospective study by Shah and colleagues [91] detected abnormal brain imaging in 95% of patients presenting with headaches compared to 13% without, implicating eclampsia as a considerable risk factor for PRES.

Definitive diagnosis necessitates confirmative imaging via MRI or CT. Either modality is effective with the former revealing the presence of bilateral hyperintensities on the posterior aspect of the cerebrum, and then frontal, cerebellum regions in specific cases (T2 weighted for MRI). An exclusionary approach is relevant to rule out pathologies that share symptoms with PRES. For example, a lumbar puncture could exclude the possibility of an infection or subarachnoid hemorrhage. Demographic qualifiers are also essential for the diagnosis of PRES, with comorbidities

shared by renal disease [88]. Physicians should be perceptive to the presence of renal dysfunction, hypertension, or recent transplantation [92,93].

3.12 Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is a rare disorder of the cerebral vasculature characterized by severe thunderclap headaches with or without neurological deficits and/or seizures [94]. RCVS is estimated to be the cause of 8–45% of thunderclap headaches in which SAH has been excluded [95]. In one large prospective study, severe headache was reported as the only symptom in 76% of patients with RCVS [96]. In patients presenting with recurrent thunderclap headaches, RCVS should be considered. Diagnosis incorporates clinical and imaging findings, in which Computed Tomography Angiography (CTA), MRI, and Magnetic Resonance Angiography (MRA) are the brain imaging modalities of choice [94]. The following clinical criteria are suggestive of RCVS: single or recurrent thunderclap headaches, multifocal segmental cerebral artery vasoconstriction typically within a week of onset, imaging findings may show FLAIR sulcal hyperintensities and/or vasogenic edema, and no evidence of aneurysmal subarachnoid hemorrhage [97].

4. Primary Headaches

4.1 Tension-Type

Tension-type headaches (TTH) are recurrent primary headaches that are characteristically bilateral, mild to moderate in severity and elapse for 30 mins to 7 days [98,99]. TTH is the most common primary headache subtype and prevalent neurological disorder in the general population [100]. Although the underlying mechanism for TTH is likely multifactorial, involving several pathophysiological etiologies including increased sensitivity of myofascial nociceptors due to both genetic and environmental causes [98]. A second hypothesis involves the sensitization of central pathway nociceptors, similarly to the first hypothesis. Other potential contributions include the dysfunctional regulatory and inhibitory capacity of the descending pain modulatory system. These include elements such as diffuse noxious inhibitory controls (DNICs) which may inhibit spatial and trigeminal neurons [101].

The usual TTH flares are characterized by bilateral, headaches with mild-to-moderate severity that are typically described by patients as “fullness around the head”, and “head dullness” [102]. The typical TTH attack presents with a non-pulsating, band-like distribution and can be further subdivided into their chronicity: Infrequent episodic TTH (<1 day per month), frequent episodic TTH (1–14 days per month), or chronic TTH (>15 days per month) [102–104]. Of note, TTH flares may less frequently present as severe, pulsating, or unilateral qualities.

Although there is no formal diagnostic work-up specific to TTH, a clinical impression reflects the International Classification of Headache Disorders (ICHD-3) criteria [105]. To fulfill ICHD-III criteria, the headache should be occurring ≥ 15 days/month on average for >3 months. In addition, at least two of these characteristics should be present: bilateral location, a non-pulsating pressure, tightening, mild to moderate intensity, and no perceived irritation from physical activities. Lastly, both must be fulfilled: No more than one photophobia, mild nausea, or phonophobia, and neither moderate or severe nausea or vomiting. This clinical diagnostic criterion considers components of headaches that may overlap with TTH, but are typically more suggestive of other headache variants, such as migraine or cluster headaches [102]. There is no neuroimaging indicated for ruling in TTH, however, patients who experience “thunderclap headaches” or other focal neurologic symptoms should receive appropriate CT or MR imaging to exclude other serious acute conditions.

4.2 Migraine

Migraines are primary headache disorders characterized by typically unilateral headaches and sometimes accompanied by debilitating auras of nausea, photophobia, and/or phonophobia [106,107]. Although the pathophysiology of migraines is complex and not entirely elucidated, migraines are believed to occur following dysfunction of meningeal nociceptors, as well as the dysregulation of vasoactive neuropeptides and activation of the trigeminal ganglion system [107,108].

The typical migraine can be subdivided into four clinical phases: (1) Prodrome and premonitory symptoms, (2) Aura, (3) Headache, (4) Postdrome [109]. The migraine aura was originally believed to precede the headache component; however, recent literature suggests it may occur concomitantly and appears in 25% of patients who suffer from migraines [110]. These auras can be characterized by focal neurologic symptoms (Table 2, Ref. [111]) and clinical caution should be applied to rule out any other acute vascular event if suspected [107]. Typically, the auras are present as scintillating scotomas, characterized by flickers of light and dark in a patient’s visual fields [112].

A typical migraine usually presents unilaterally and can last up to 24 hours, though rarely they may elapse longer than 3 days [106,107]. Migraines are usually described as “pulsating”, “throbbing”, or “pounding” pain. Outside of the visual auras which can present with migraines, nausea and severe phonophobia can also occur [107]. Patients will report seeking relief from the debilitating pain of migraine by lying down in a quiet, dark room, thus often alleviated with sleep [113,114]. Overall, migraine affliction can leave those affected with severe disability the extent of bed rest as described. Indeed, in a nationwide survey by Waliszewska and colleagues [115], 3225 patients were assessed with nearly 75% reporting necessity of bed rest dur-

ing the period of the episode. As the headache resolves, patients may experience a prodrome normally marked by neck pain, usually exacerbated with movement or activity. Patients may also feel fatigued or have trouble resuming daily activity [116,117].

Like other primary headache variants, migraine headaches can be clinically diagnosed by integrating a clinical history and physical exam suggestive of migrainous features [105]. Although like tension headaches, the most unique presentation to migraine headaches will include auras—particularly those with photophobia, phonophobia, nausea, and vomiting—as well as a headache exacerbated by activity. The International Classification of Headache Disorders, ICHD-3, has a delineated criterion for migraine headaches, depending on whether the migraine presents with auras [105]. Migraines with aura are diagnosed by at least two attacks with one or more reversible aura symptoms (visual, sensory, speech, motor, brainstem, or retinal), and at least 3 of the following characteristics: Aura symptom spreads gradually over 5 minutes, 2+ symptoms occur in succession, each symptom lasts 5-60 minutes, at least one aura symptom is unilateral, at least one aura symptoms is positive, and the aura is accompanied with a headache. Migraines without aura are diagnosed by at least 4 attacks lasting 4-72 hours with either nausea/vomiting, photophobia/phonophobia, or both, and at least two of the following features: unilateral location, pulsatile quality, moderate or severe pain, aggravation or causing avoidance of routine physical activity [105].

4.3 Cluster

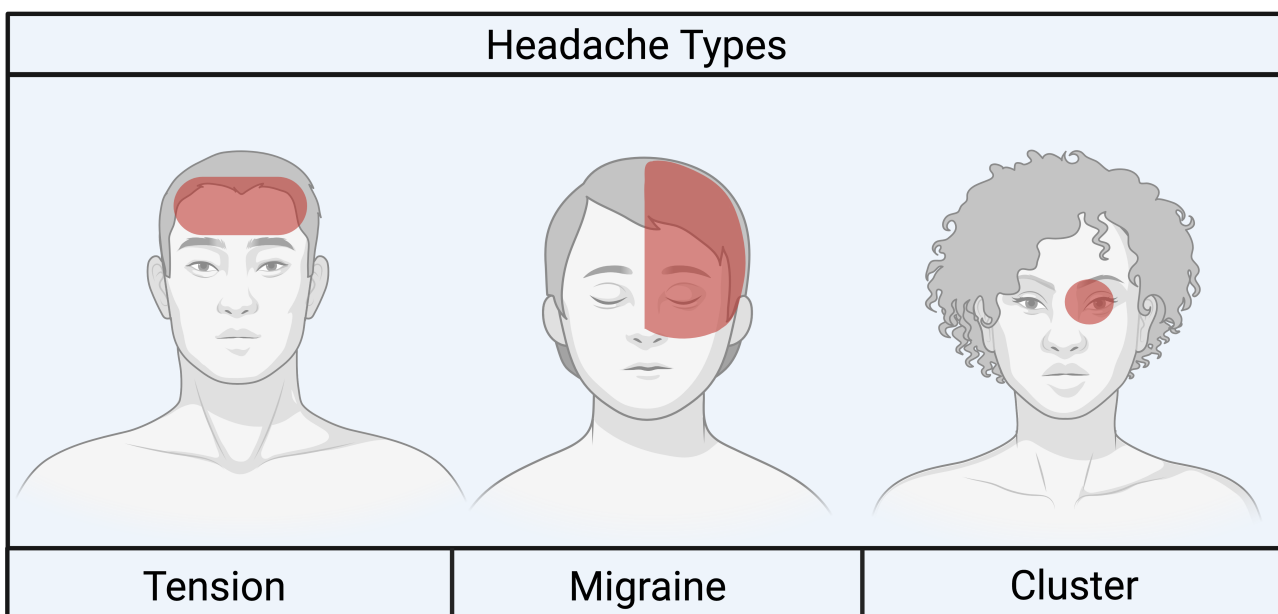
Cluster headaches are classified as trigeminal-autonomic cephalgia, characterized by severe unilateral pain on the head and face (Fig. 2) with accompanying ipsilateral autonomic cranial symptoms (flushing, lacrimation, rhinorrhea) [118,119]. It is suspected that the first branch of the trigeminal nerve becomes activated and starts an inflammatory cascade, leading to pain.

Clinically, cluster headaches have variable presentation but are mostly seen in males between the ages of 20 to 40 years [120]. When considering ICHD-III criteria, a patient will report experiencing excruciating unilateral craniofacial pain, autonomic symptoms on the same side as the pain, and agitation [121]. These headaches are characterized by their cyclical nature: periods of weeks to months of experiencing severe pain followed by remission. Remissions can last months to years, with some reporting no return of their symptoms [120]. During attacks, the headaches can last up to three hours and reoccur multiple times a day, with reports of up to eight episodes in a single day [122]. While cluster headaches can present like migraines, patients will want to pace or apply pressure onto the painful area to “lessen the intensity” [123].

People that suffer from cluster headaches often spend years without receiving a diagnosis. This is due to mul-

Table 2. Common migraine aura subtypes with description.

Description of common migraine aura subtypes	
Subtype	Subtype description
Visual	Visual auras are the most common and typically begin as a small scotoma affecting the point of visual fixation. These visual deficits are transient and can progress to affect a larger visual field and may be unilateral or bilateral. Geometric shapes or floaters may also occur, usually in a C-shape, and may be of “shimmering” qualities in peripheral visual fields.
Sensory	Sensory auras are also commonly associated with migraines and (usually) may follow visual auras. These typically begin as unilateral paresthesia of the face or an extremity but may proceed across the midline and be accompanied by transient numbness. It should be noted that an aura is very characteristic of a migraine and is atypical of an acute vascular event when it begins with a slow progression of positive symptoms (paresthesia) followed by negative symptoms (scotomas, numbness).
Language	Language auras are less common but may range from mild anomic aphasia of mild wording retrieval difficulty to frank dysphasia with paraphasic errors.
Motor	Motor auras are atypical migraine auras and can be characterized from any unilateral face or extremity weakness to fully developed hemiplegic migraine, involving multiple extremities, though these typically express a genetic basis.

**Fig. 2. Pain distribution of tension-type, migraine, and cluster headaches.**

multiple factors, ranging from lack of access to healthcare to decreased clinician awareness [120]. Unless the patient presents with an active episode, a neurologic exam will be unremarkable. Neuroimaging and vascular imaging are used to rule out any structural or neoplastic etiologies. Once a thorough history is collected, and secondary causes are ruled out, the diagnosis of cluster headache can be made.

4.4 Exertional

Exertional headaches tend to be more acute and assessed in emergency settings [124]. Patients who present with exertional headaches report experiencing bilateral throbbing cephalgia after engaging in any physical activity. The pain occurs after activities that increase intra-abdominal pressure and is commonly bilateral, posterior, but short-lived. These activities can include coughing, ex-

ercise, and sexual activity. Though the onset of each may be attributable to physical activity, each has its own unique etiology described in the following discourse.

Primary cough headaches are generally a rare finding, usually seen as secondary to another intracranial finding [125]. Patients with primary cough headaches are usually above 40 years of age and report other symptoms such as nausea or vertigo [126]. Primary headaches secondary to exercise is described as bilateral, throbbing, and always follows sustained physical exertion. It is more likely to occur during hot weather or at high altitudes. While the exact pathophysiology is unknown, it is thought to originate from a vascular disorder that is not otherwise specified, creating friction on sensitive cerebral structures [127]. Coital primary headaches are triggered during or after sexual activity [124]. This primary headache syndrome may be underre-

ported due to discomfort discussing sexual activities. The pain is bilateral and may be abrupt or dull. Patients are usually males in their 20s and 30s [128].

For all three types of exertional headaches, the pain will present after the specified stimulus that triggers it. The severity of the pain is variable but tends to be bilateral. A diagnosis of exertion headache can be made with history; however, due to the acuity of the pain, most patients present in emergency settings. Subsequently, secondary etiologies of headache are investigated with neuroimaging and lab studies [124,128].

4.5 Primary Headache Treatments

In patients experiencing chronic or debilitating TTH, prophylactic treatment is indicated [114,129]. The goals of preventive therapy are to reduce TTH flares frequency, duration, and severity, and to improve the efficacy of other therapeutics during acute flares [129]. Support evidence suggests that the most efficacious agent for prophylactic management of chronic TTH is the tricyclic antidepressant amitriptyline [130,131]. Additionally, the anticonvulsants topiramate and gabapentin have been shown to reduce TTH flare frequency [131]. Management of acute TTH attacks includes the use of non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. A single dose of ibuprofen 400 or 600 mg daily in conjunction with aspirin 500 to 650 mg daily has shown effective management for mild to moderate symptom burden [131].

Preventive treatment of migraine headaches is tailored to any precipitating factors specific to the patient which are modifiable [132]. That is, often, patients who have trigger stimuli (e.g., lights, loud sounds, foods) may tailor their goals to reducing the frequency and duration of these migraines by identifying and modifying their exposure to these triggers. The first line of pharmacotherapy for migraine headaches includes NSAIDs, aspirin, acetaminophen, and perhaps a combination with caffeine to alleviate acute flares [114,132]. For more chronic or severe headaches, parenteral antidopaminergics, such as metoclopramide, or migraine-specific medications such as sumatriptan, may be considered [133,134]. In many cases, comorbid conditions can help tailor the choice of medication regimen. For patients with hypertension who are non-smokers and less than 60 years of age, beta-blockers may be reasonable options [133]. For patients with major depressive disorder (MDD) or other mood disorders, some possible medications include amitriptyline or venlafaxine. Additionally, patients with epileptic disorders may benefit from valproate or topiramate [135].

Lastly, the first line treatment for cluster headaches is verapamil, titrated according to patient response [121,136]. Unfortunately, no evidence shows that interventions prevent recurrence [121]. Regarding emerging treatments, several of these are being incorporated into therapeutic landscape, namely monoclonal antibody therapy. Mono-

clonal antibody therapy has been utilized as a less conventional outlet, though these primarily involve calcitonin gene-related peptide (CGRP) such as erenumab and fremanezumab, among others [137]. Briefly, the mechanism of these antibodies are based on the implicated role of CGRP. CGRP is reported to be a 37 amino acid peptide native to the central nervous system (CNS) and the peripheral nervous system (PNS), contributive to cerebral vasodilation [138]. These are considered in instances refractory to first- and second-line treatments such as beta-blockers [139]. Other downstream therapies may include onabotulinumtoxinA which are typically likewise reserved for refractory cases [137]. OnabotulinumtoxinA carries several potential roles which have been suggested to mitigate migraine symptoms, one of these being inhibition of nociceptive pain. It has displayed the ability to decrease exocytosis of glutamate towards fibers which transmit these signals [140].

5. Conclusion

Headache contributes to a significant proportion of patients presenting to the emergency department. Though most of these patients are affected with primary headaches, it is mandatory to exclude malignant secondary processes. Careful history and physical examination will help avoid misdiagnosis in these patients. Neuroimaging and CSF/serum testing can assist for a more accurate diagnosis and subsequent selection of treatment.

Author Contributions

JH wrote the initial outline, abstract, introduction, the initial evaluation/acute bacterial meningitis, temporal arteritis, and revisions. EM wrote the idiopathic intracranial hypertension, tension-type, migraine sections. AR wrote exertional, cluster, Table 1, and formatting/revisions. SW wrote tumor, acute ischemic event, Fig. 2, and revisions. AN wrote unruptured vascular malformation, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, primary headache treatment, Table 2. GP created Fig. 1, assisted in initial draft formatting, and wrote revisions. BLW provided feedback on the initial outline and edited the drafted manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

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