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REVIEW ARTICLE

Headache and Its Approach in Today's NeuroIntensive Care Unit

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Abstract Headache is a very common symptom in the neurointensive care unit (neuroICU). While headache in the neuroICU can be caused by worsening of a pre-existing primary headache disorder, most are secondary to another condition. Additionally, headache can be the presenting symptom of a number of conditions requiring prompt recognition and treatment including subarachnoid hemorrhage, ischemic and hemorrhagic stroke, central nervous system infection, pituitary apoplexy, and cerebral vasoconstriction. The neuroICU also has a unique postoperative population in which postcraniectomy and postcraniotomy headache, postintravascular intervention headache, hyperperfusion syndrome, ventriculitis, medication overuse or withdrawal headache, and hypercapnia may be encountered. Management varies dramatically depending on the etiology of the headache. Overreliance on opiate analgesics may produce significant adverse effects and lengthen ICU stays. However, nonnarcotic medications are increasingly being recognized as helpful in reducing the pain among various postsurgical and headache patients. Taken together, a multimodal approach targeting the underlying pathology and choosing appropriate systemic and local analgesic medications may be the best way to manage headache in critically ill patients.

Keywords Headache · Intensive care unit · Neurocritical care · Multimodal approach · Headache management

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Introduction

Headache is the most commonly reported neurological complaint and can be severely disabling. The underlying causes of headache are myriad and include primary and secondary headache, a distinction described in the International Classification of Headache Disorders 3rd edition, beta version [1]. Of the primary headache disorders, migraine is well known and affects 30–40 million individuals in the United States alone [2, 3]. Primary headache syndromes have been described in detail in other review articles. However, the impact and recognition of secondary headaches, particularly in the intensive care unit (ICU) settings, also warrant clinical attention, and will be the focus of this review article. Secondary headache disorders are easily misdiagnosed as primary headache, while actually reflecting more ominous and emergent underlying pathologies. Likewise, headache as a symptom in critically ill patients may be a harbinger of impending and rapid neurological decline and should lead the neurologist to consider secondary causes. In the neuroICU, headache may have various causes, some of which are summarized in Fig. 1.

Epidemiology and Impact of ICU Headache

Epidemiological studies examining the prevalence of headache among patients admitted to the ICU is scant.

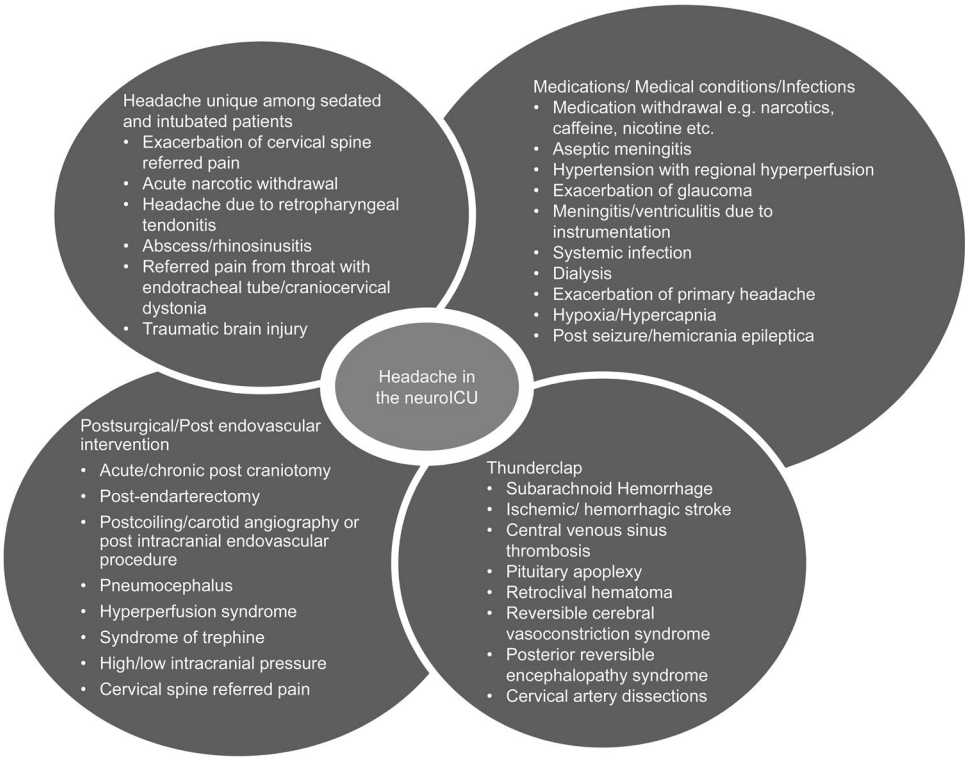

Fig. 1 The classification of NeuroICU headache includes multiple disease states. While this list is not exhaustive, it includes four major categories of headache that may be frequently encountered: headache following surgical and endovascular intervention, headaches accompanying substance withdrawal, medical illness, and infection, headache following intubation, and sedation and thunderclap headaches

These patients therefore represent an understudied population. One published abstract by Vukasinovic et al. presented to the 4th European Headache and Migraine Trust International Congress evaluated the prevalence of headache in a population of patients admitted to the ICU in Nis, Serbia, and found that between 1997 and 2013, 2237 of the 4941 patients with cerebrovascular disease presented with headache as part of their initial symptomatology. When examining individualized incidence rates of various neurological emergencies with accompanying headache, it is not surprising that over 40 % of patients in the neuroICU have headache [4]. Of the headaches encountered, thunderclap headache (TCH) is most worrisome for subarachnoid hemorrhage (SAH) and is a common cause for ICU admission. In one prospective study, severe TCH occurred with an incidence of 43 per 100,000 persons older than 18 years. While in most cases, there was no life-threatening event identified, 11 % had SAH [5]. Sentinel headache is often described as thunderclap-like and precedes radiographic evidence of SAH. This type of headache is likely caused by a warning leak from an aneurysm and occurs in about 10–43 % of patients who will go on to develop SAH [6, 7]. With annual incidence rates of SAH estimated between six and 21 per 100,000, this type of headache makes substantial contributions to ICU admissions [8–10]. Furthermore, headache occurs in approximately 20–30 % of patients at the onset of stroke [11]. Approximately, 30 % of ischemic stroke and 60 % of hemorrhagic stroke patients will report a headache at some point during the acute phase [12, 13]. Moreover, neurointensivists and neurosurgeons frequently confront postneuroendovascular and postcraniectomy headache. In one study, 25 % of patients suffered new or worsening headache following coil embolization of an unruptured intracranial aneurysm [14]. A second study cited much higher rates of postprocedural headache—up to 70 % including those who had glue embolization and stent deployment [15]. Despite the common occurrence of ICU headache, it is unclear which patients are at risk of developing chronic headache conditions after they are discharged. It is estimated that as many as 10 % of stroke patients presenting with headache at onset will go on to develop chronic headache [16].

Headache as a symptom in the neuroICU has a potentially profound impact on patient care, often resulting in increased utilization of radiographic imaging modalities, invasive procedures such as repeat conventional angiograms, and the use of sedating analgesics. Increased utilization of these resources may increase the length of hospital stay and reduce mobilization and early recovery. In one study, headache was the second leading cause of 30-day readmission following ICU admission for SAH [17]. Although escalating headaches in the ICU require immediate evaluation and treatment, developing algorithms for patient management and treatment dilemmas, like whether to use opiate or nonopiate analgesics, remains an important challenge [18].

Mechanism of Headache

Although the brain parenchyma is insensitive, various intracranial, calvarial, and cervical structures are pain-sensitive [19]. Nociceptive afferents of the trigeminal and upper three cervical spinal nerves converge onto second-order neurons in the trigeminal cervical nucleus in the upper cervical spinal cord and brainstem (Fig. 2). Pain-sensing fibers of the trigeminal ganglion not only innervate bone, skin, and muscle tissues of the head and neck but also innervate meningeal vessels and proximal intracranial vessels including those of the circle of Willis. Ischemic stroke may precipitate stimulation of peptidergic pial and perivascular nerve fibers of trigeminovascular afferent origin [20]. Other mechanisms of headache have been proposed, including changes in the caliber of occluded arteries, especially in subcortical strokes [21]; disturbance in blood flow; dilation of pain-sensitive collateral vessels [22]; and stimulation of sensory afferents of the trigeminovascular system either directly by ischemia or indirectly by cortical spreading depression (CSD) [23]. Lastly, headache could also result from injury-evoked degranulation of calvarial/periosteal mast cells which can lead to a meningeal inflammatory response [24].

General Approach to Headache in the NeuroICU

The first step in approaching headache in the ICU is obtaining a history [25]. The description of the headache, including pain quality, severity, location, duration, and speed of escalation, is critically important. A severe, explosive headache with rapid onset—the definition of TCH—might be a clue to a potentially perilous neurological illness. The causes of TCH vary from SAH, reversible cerebral vasoconstriction syndrome (RCVS), parenchymal hematoma, ischemic stroke, venous thrombosis, pituitary apoplexy, vessel dissection, and spontaneous intracranial hypotension [26]. Accompanying symptoms of transient or fixed neurological deficits, vomiting, fever, neck stiffness, and changes in level of alertness amplify the likelihood of an underlying infection like meningoencephalitis. A history of prior headache may be important but should not dull the clinical suspicion for secondary headache [27–30]. The

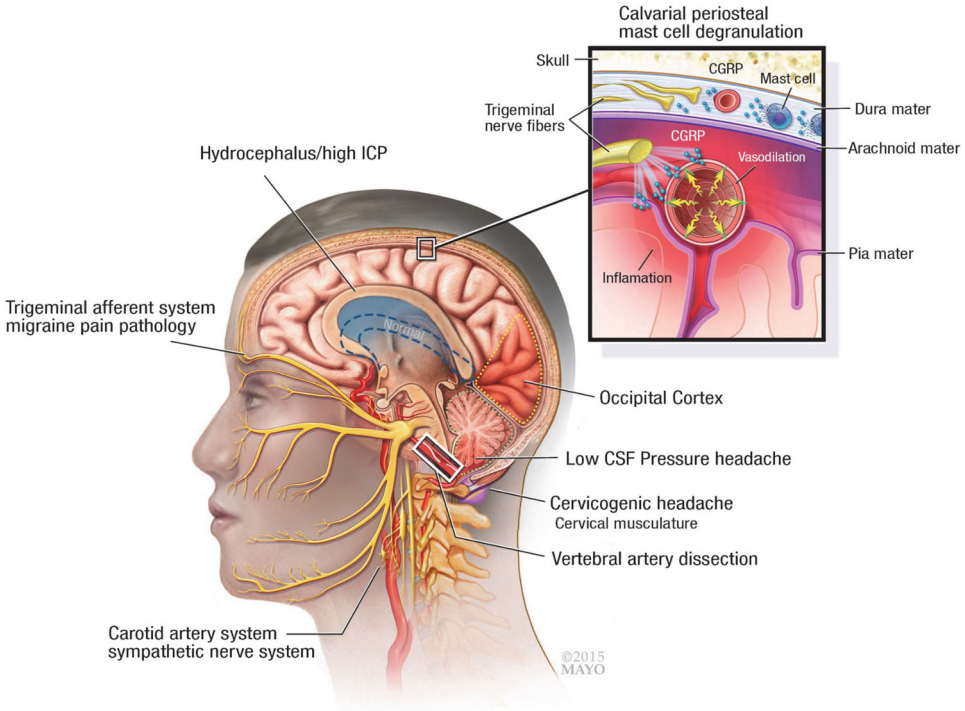

Fig. 2 Pathophysiology and mechanism of headache. Nociceptive information from trigeminal and trigeminovascular nerve fibers innervating skin, head, and neck muscles, calvarial and bony tissues, and intracranial and extracranial blood vessels are likely to be activated and sensitized in a number of neurological conditions that produce headache in critically ill neurological patients. Release of vasoactive substances like calcitonin gene-related peptide in the meninges, degranulation of mast cells, and mechanical activation of perivascular afferent fibers may contribute to persistent headache. Calcitonin gene-related peptide (CGRP), cerebrospinal fluid (CSF). By permission of Mayo Foundation for Medical Education and Research. All rights reserved

unique environment of the neuroICU and the degree of illness may limit the ability to gather these details. However, the setting within which the headache occurred—for example, following endovascular procedure, difficult intubation with hyperextension of the neck, valsalva, trauma, or motor vehicle accident—may heighten the suspicion for dissection, raised intracranial pressure, or new or worsened aneurysmal rupture.

A thoughtful physical examination is similarly important for limiting the differential diagnosis. The examiner should look for both obvious deviations in normality as well as subtle signs of pathology. Examination findings that may aid in the differential diagnosis include new cardiac murmurs or rubs and cervical bruits [31]. Cranial auscultation, particularly in the setting of a proptotic or chemotic eye, may help localize carotid cavernous fistula (CCF) as will recognition of arterialized conjunctival vessels [32]. The ophthalmological examination and pupillary light response is also important in suspected dissection, aneurysms, and cavernous sinus syndromes. Painful Horner's syndrome with the triad of ptosis, miosis, and anhidrosis can accompany carotid artery dissection but can be subtle and incomplete [33, 34] (Fig. 3). Individuals presenting with TCH and third-nerve palsy with pupil involvement should raise suspicion for rupture of a posterior communicating artery aneurysm. In contradistinction to the pupil asymmetry of Horner's syndrome, the pupil involvement associated with this aneurysm results from excessive dilation due to compression of the extrinsically located parasympathetic fibers traveling along the third nerve. Additional combinations of cranial nerve findings such as involvement of third, fourth, sixth, and the first and second divisions of the fifth cranial nerves may insinuate cavernous aneurysms, cavernous carotid fistula, pituitary apoplexy, or worsening cavernous sinus infection. Lastly, evaluating for worsening or new focal neurological deficits that may accompany recurrent or worsening headaches, particularly following SAH, may be a clue to vasospasm, recurrent bleeding, Todd's paralysis following focal seizure, ischemic stroke, or raised intracranial pressure.

Evaluating and Measuring Headache Intensity

The headache assessment should be performed repeatedly during the ICU admission to determine if there is an escalation of pain intensity or if a new headache arises. This often requires a multidisciplinary team, the assistance of nursing staff, and sometimes pain management specialists. If a patient is able to report pain, self-assessment and description of the headache is a reliable method for tracking symptoms and their response to treatment. Pain levels can be assessed in the self-reporting population with one-dimensional tools like the numeric rating scale (NRS) or visual analogue scale (VAS) at rest and with provocation (deep breathing, cough, and mobilization). Both tools are more powerful in detecting changes in pain intensity than the verbal categorical rating scale [35]. Scales should not replace the description of the headache quality or nature, as a change could assist in diagnosing new pathology (such as a postprocedural CSF leak).

In patients who are not able to reliably report pain due to a depressed level of alertness, other measures can be employed [36]. These measures, while not headache specific, are reliable and include the Behavioral Pain Scale (BPS) and Critical Care Pain Observation Tool (CPOT). They combine facial expression, motor movements, ventilator compliance, and vocalization and can be used in place of self-reporting assessments for patients who are unable to self-report [37]. While changes in vital signs can accompany these behavioral assessments and self-reporting tools, they should not be used in isolation to treat or diagnose pain.

Specific Headache Entities

Thunderclap Headache

TCH is a severe, acute, explosive headache that immediately reaches maximal intensity. The headache can last hours to days and can be recurrent. The term TCH was coined by Day and Raskin in the 1980s because of its dramatic presentation as if being struck by a thunderbolt or thunderclap [38]. A similar phenomenon was likely also described by C. Miller Fisher as a "crash migraine" [30]. Traditionally, this is the prototypical headache accompanying SAH and aneurysmal rupture. However, it can also be experienced with unruptured aneurysms [39]. TCH can accompany multiple neurological conditions including vasculopathy, venous thrombosis, dissection, colloidal cyst, and intracranial hypotension [40, 41]. In a recent systemic review, 27 % of TCH was due to primary headache disorder, 17 % was due to cerebrovascular disease, and less than 1 % was related to other causes [42].

Subarachnoid Hemorrhage

The incidence of SAH is 5–10 per 100,000 person-years and the most common cause is ruptured intracranial aneurysm. Eighty-five percent of SAH is attributed to saccular aneurysmal rupture. A smaller percentage is nonaneurysmal and often perimesencephalic. Additional causes of SAH include trauma, arteriovenous malformation, dissection, and amyloid angiopathy [43] (Fig. 4b).

TCH is the primary symptom and the symptom most reliably described by virtually all patients with SAH [44].

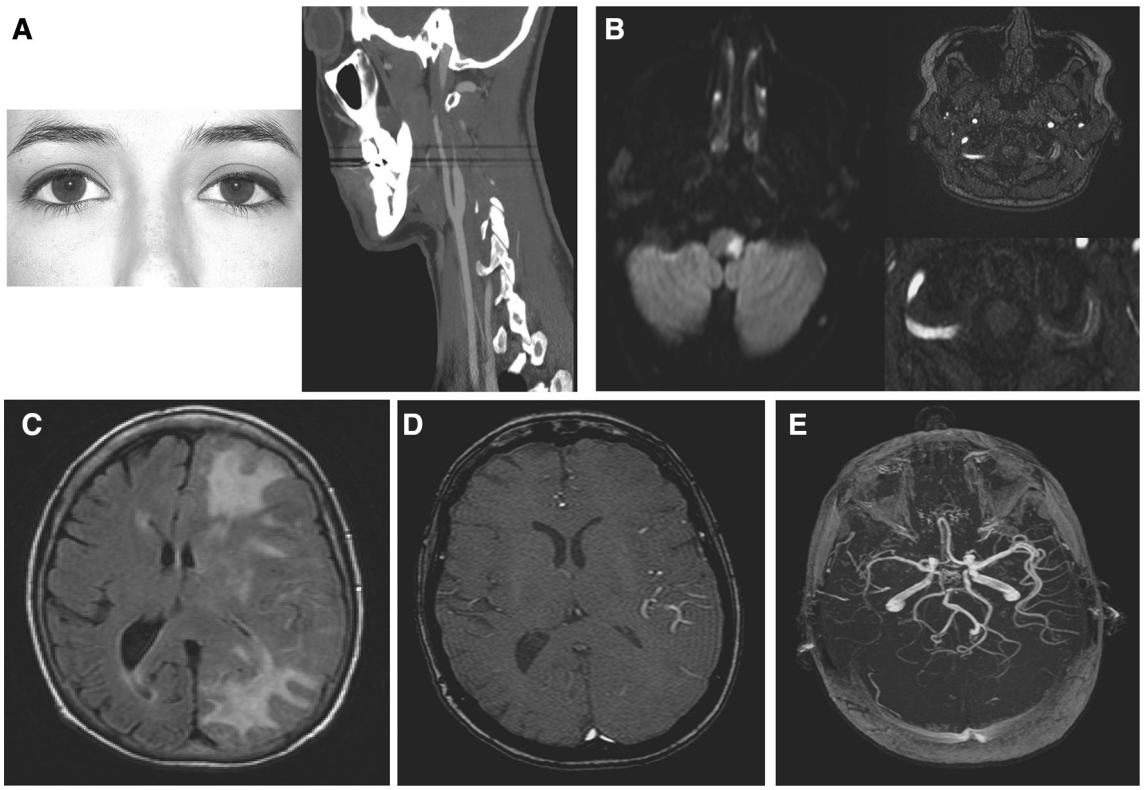

Fig. 3 Headache accompanying ischemic stroke and carotid revascularization. **a** Cervicocephalic dissection. **a** Horner's syndrome in the setting of a left carotid artery dissection. Twenty-six-year-old woman with a history of migraine without visual aura presenting with left hemicranial severe sharp pain located behind the eye, in the ear, and radiating to the jaw described as someone running a nail through her head with accompanying sensitivity to light and sound. Physical examination reveals a subtle left upper eyelid ptosis and miosis. CT angiogram reveals a flame-shaped tapering of the left internal carotid artery. **b** Thirty-one-year-old presenting with sharp occipital headache, vertigo, and gait imbalance was found to have a left Horner's syndrome, left arm and leg weakness, ataxia, left hemibody decreased soft touch sensation, right hemibody decreased pinprick sensation, and hiccups. Diffusion weighted imaging demonstrated a left lateral medullary infarct, and MR angiogram revealed a left vertebral artery dissection. **c** Cerebral hyperperfusion syndrome following left carotid endarterectomy. The patient developed headache and right hemiplegia. **d**, **e** demonstrates enlargement of the anterior, middle, and posterior cerebral vessels compared to the right

Nausea, vomiting, and pulsations have been described with these headaches. SAH is present in about 25 % of patients presenting with TCH in the Netherlands and is associated with aneurysm in 14 %. SAH was found in 12 % of those who presented with TCH as their only symptom [7, 26].

The pain associated with aneurysmal rupture may be related to stretching of the blood vessel wall. However, in the case of nonaneurysmal rupture, other potential etiologies are likely to exist, including increased local inflammation and irritation of the surrounding blood vessel, chemosensitive nerve endings innervating the adventitial wall, meningeal irritation and inflammation, or vasospasm and mechanical stimulation of trigeminovascular afferents. While the most compelling hypotheses are vascular, other neurogenic mechanisms may also be involved [26]. In our clinical practice, it appears that there are different observed phases to SAH headache. The first phase occurs acutely at the instance of leak or rupture and is likely related to stretching of the blood vessel or meningeal irritation. The second and third phases occur later and may be related to vasospasm and worsening aseptic meningitis as the blood products are broken down. However, the rebleeding of an aneurysm can also occur, leading to recurrent TCH after the initial event [18]. In terms of outcome measures, there are various rating scales that can help predict the mortality rate associated with SAH.

The treatment of headache following SAH in the acute setting may include opiate analgesics. However, these have the potential for adverse effects including respiratory depression, decreased level of alertness, and gastrointestinal dysmotility. Calcium channel blockers, namely nimodipine, have been used in primary TCH and are beneficial for reducing the risk of cerebral vasospasm [45, 46]. Calcium channel medications may be administered intravenously and transitioned to an oral form after discharge and can be continued for up to 21 days [47, 48]

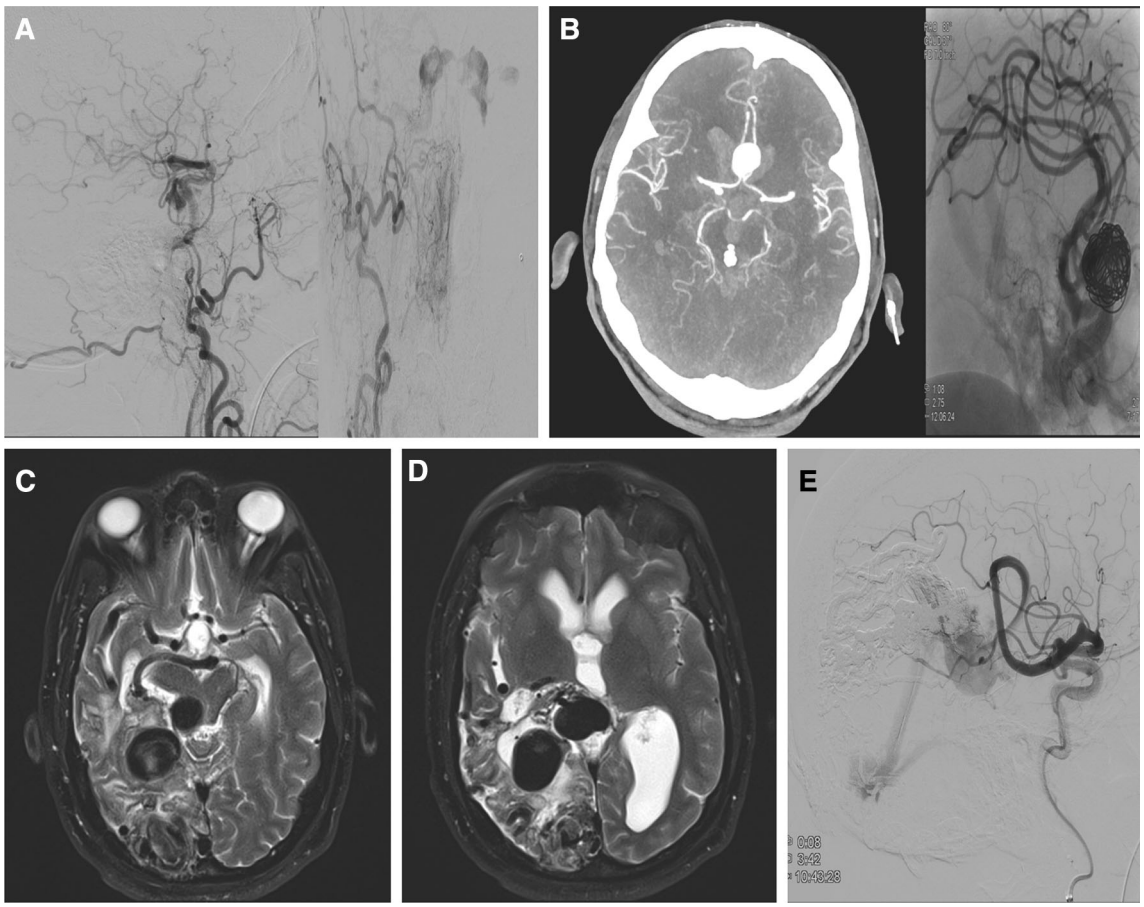

Fig. 4 Headache accompanying vascular malformations and cerebral aneurysm. **a** Carotid cavernous fistula. Low-flow, indirect carotid cavernous fistula demonstrating arterial feeding vessels from the right external carotid artery (likely ascending pharyngeal artery branches). The fistula arises from the wall of the right cavernous sinus and drains across the intercavernous portion to the left cavernous sinus, left superior ophthalmic vein, and right and left facial veins. **b** Aneurysmal rupture. Thunderclap headache in the setting of giant anterior communicating artery aneurysm that ruptured, producing diffuse vasospasm. **c–e** Arteriovenous malformation. Middle-aged man presenting with worsening seizures, migraine-like headaches with visual aura, left homonymous hemianopia, left leg weakness, and encephalopathy found to have a large AVM with mass effect on the dorsal midbrain with aneurysm formation. Onyx embolization resulted in partial reduction of the AVM. Obliteration of the AVM was not deemed possible due to the size of the lesion

especially for nimodipine. Gabapentin enhances GABAergic signaling and modulates calcium channels. It has been used for the treatment of primary TCH [49]. Gabapentin appears to be well tolerated and can be safely administered in patients with SAH. Further data are needed to test the hypothesis that gabapentin can significantly reduce acute and chronic pain associated with SAH. However, based on our preliminary data, it may be useful in decreasing opiate analgesic requirements and VAS scores [18]. Interestingly, headache associated with SAH can respond to triptans, serotonin 1B/1D receptor agonists used as abortive agents in the treatment of migraine [50]. In general, these medications should be avoided in conditions that could precipitate or result from vasospasm or vasoconstriction due to the impact of the 1B receptor subtype. Therefore, it is theoretically not considered safe for use in SAH and should not be administered. It is unclear as to why triptans alleviate the headache associated with SAH. One potential explanation is that the 1D receptor is not only located on nerve fibers that course along large extracranial but also intracranial blood vessels including those in the proximal circle of Willis [51]. Other possible explanations for this drug effect include reduced meningeal irritation.

Pituitary Apoplexy

Pituitary apoplexy is caused by acute hemorrhage or infarction of the pituitary gland. This usually occurs in the setting of a pituitary adenoma but can occur in the postpartum period as well. The headache associated with this neurological emergency is severe and thunderclap in

nature. The headache may be accompanied by meningeal symptoms, such as nausea and vomiting. If the hemorrhage extends into the cavernous sinus, cranial nerves three, four, six and the first and second divisions of cranial nerve five may also be involved. The apoplexy associated with a pituitary adenoma may result from raised intrasellar pressure if the tumor rapidly enlarges. Local inflammatory change may also contribute to bleeding. Surgical evacuation of the hemorrhage and adenoma if present can alleviate the pressure and may alleviate the headache as well [52].

Venous Sinus Thrombosis

Up to 10 % of cerebral venous sinus thrombosis (CVST) presents with TCH. The headache accompanying CVST tends to be persistent and is worsened with Valsalva maneuvers or activities that raise intracranial pressure. Thrombus formation in the cerebral veins can occur spontaneously. However, it may be the result of a pre-existing condition that increases the propensity for thrombus formation such as protein C and protein S deficiencies, Factor V Leiden deficiency, or malignancy. Other potential contributing factors include oral contraceptive use and dehydration. Hemorrhagic and ischemic strokes, focal neurological deficits, and seizures may accompany CVST. The treatment for CVST includes initiation of anticoagulation. While counterintuitive, starting anticoagulation can reduce the progression of disease even in the presence of hemorrhagic stroke [41, 53].

Low-Pressure Headache

Low-pressure headaches can follow craniotomy, craniectomy, transsphenoidal, or minimally invasive procedures, and spinal surgeries. Spontaneous intracranial hypotension has been observed in those with hypermobile joint disorders [54]. The most distinguishing feature of low-pressure headache is its precipitation with upright posture and thunderclap-like quality [55, 56]. The headache may be accompanied by transient cranial nerve six palsy [56]. Additional distinguishing features that may or may not be present include tinnitus, auditory muffling, interscapular pain, or upper extremity radicular pain [41]. From a diagnostic perspective, low opening pressure is often noted with lumbar puncture, and diffuse pachymeningeal enhancement and sagging of the brain can be observed on MR imaging. Myelogram may reveal the location of the leak [54]. Initial conservative therapy with rest and hydration, including caffeine intake, can help alleviate the pain. If the pain is refractory, blood patch and, if needed, duraplasty may be helpful [57].

Headache Associated with Vascular Lesions and Malformations

Vasculopathy and Vasculitis

Central nervous system (CNS) vasculitis, an inflammation of the blood vessel wall, and vasculopathy related to either vasospasm or vasoconstriction are a heterogenous group of disorders that can either occur solely within the brain as a primary CNS process or as a secondary consequence of a more systemic disease process like lupus erythematosus, polyarteritis nodosa, Churg–Strauss syndrome, and other autoimmune-related conditions. Primary or isolated CNS conditions include RCVS, primary CNS angiitis, and venous vasculitis.

Reversible Cerebral Vasoconstriction Syndrome RCVS, also termed Call-Fleming syndrome [58], is a reversible, segmental narrowing of cerebral arteries. RCVS typically presents with severe recurrent TCH and can last up to 12 weeks [26]. In one study, TCH was observed in 85 % of patients as an initial and recurrent symptom [59]. RCVS has a predilection for women between the ages of 20 and 50, with a median age of 40 [59]. If severe, RCVS can result in seizures, acute ischemic stroke or intracranial hemorrhage from reduced blood flow and dysregulation of arterial tone. In one case study examining 59 patients with RCVS, approximately 30 % had rapid clinical deterioration within 2–3 days of their initial diagnosis. Eight of 20 had permanent deficits, and four of 20 died as a result [60]. The syndrome may be associated with the use of vasoactive substances and the postpartum state. There appears to be an association between RCVS and the use of serotonin reuptake inhibitors, nasal decongestants, and marijuana, all of which should be avoided in patients with RCVS [61].

CNS Vasculitis Primary CNS angiitis or granulomatous angiitis of the central nervous system (PACNS) is a rare and often fatal condition [62] presenting with a wide array of neurological symptoms from confusion and obtundation to hemiparesis. Pathology from tissue biopsy and autopsy often reveals lymphocytic, epithelioid, and histiocytic transmural inflammation of the blood vessel wall with the presence of multinucleated giant cells [63]. Neuroimaging reveals a beaded vasculopathy and subcortical white matter disease, hemorrhage, and cerebral edema (Fig. 5). PACNS can be differentiated from RCVS as it tends to be a more insidious headache and may be associated with elevations in systemic inflammatory markers, cerebrospinal fluid (CSF) white cell count, and protein [41].

Corticosteroid and other immunosuppressive agents may be used for the treatment of noninfectious vasculitis and vasculopathy related to autoimmune disease, which may

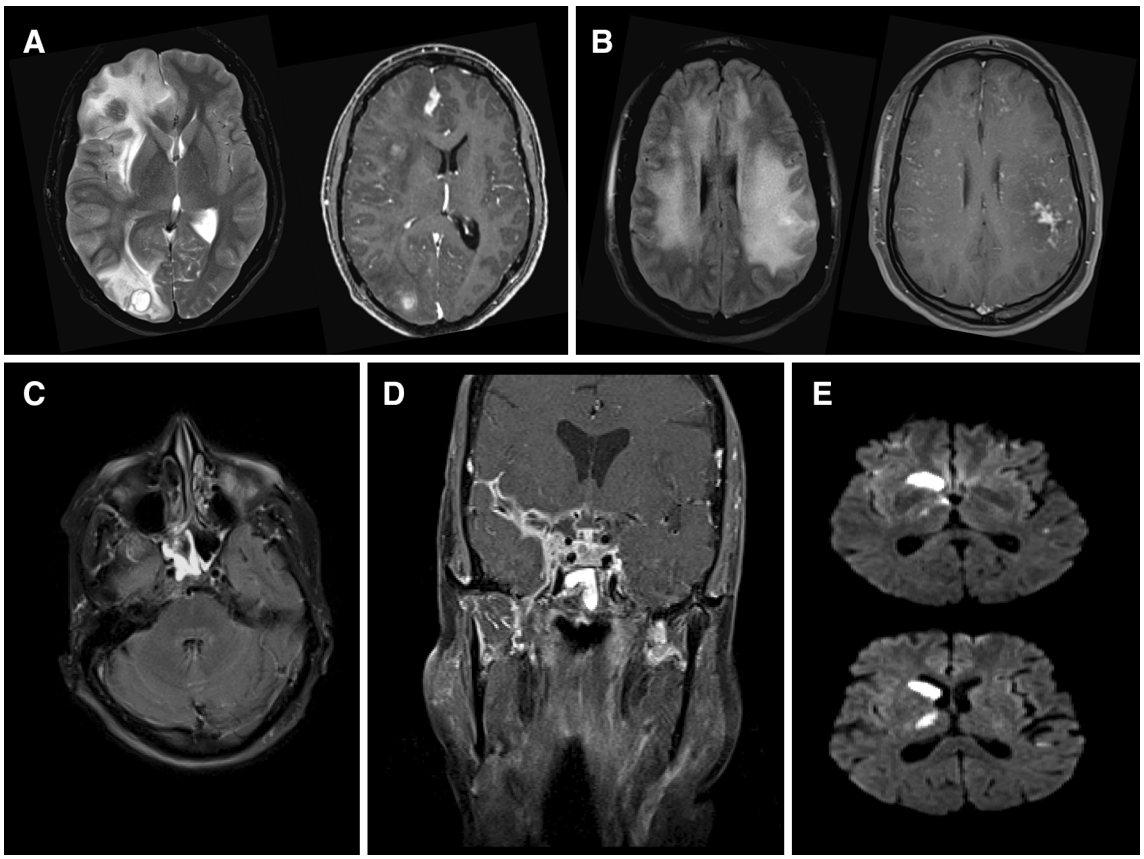

Fig. 5 Headache related to CNS infectious and inflammatory diseases. **a** CNS thrombophlebitis. Twenty-five-year-old man with a viral prodromal illness described as low-grade fevers, chills, and rash who developed holocephalic headache, tonic–clonic seizure, left upper extremity weakness, paresthesias, and left homonymous hemianopia. He was found to have right frontal and parietal complex and cystic T2 hyperintense lesions with vasogenic edema and enhancement. Histopathology of a right frontal lobe specimen revealed obliterating vasculitis with a predilection for large meningocerebral veins and small parenchymal venules with acute and chronic thrombosis. **b** CNS angiitis. Twenty-five-year-old woman presenting with headache and aphasia was found to have nodular sclerosing classic Hodgkin's lymphoma. MRI of the brain revealed diffuse subcortical hyperintense lesions with parenchymal enhancement. Histopathology revealed cerebral angiitis. **c**, **d** Fungal sinus infection. Aspergillus infection in the right sphenoid sinus with extension into the right cavernous sinus, with pial and dural involvement including probable epidural abscess of the anterior medial right middle cranial fossa and basilar meningitis presenting with thunderclap-like headaches, cranial neuropathies, and encephalopathy. **e** Focal neurological deficits can be a clue to angioinvasion of fungal vasculitis as demonstrated in this example with later involvement of anterior and middle cerebral arteries causing ischemic stroke with restricted diffusion in the ipsilateral caudate and posterior limb of the internal capsule

improve the headache symptoms. Calcium channel blockers like nimodipine or verapamil have been used for the treatment of RCVS as well; although, it is unclear if they improve outcome or alter the headache associated with RCVS [59]. In general, serotonergic and vasoactive medications like pseudoephedrine should be avoided.

Carotid Cavernous Fistula

CCF is a communication between the cavernous internal carotid artery and venous structures in the cavernous sinus. The syndrome associated with CCF usually involves periorbital pain. Depending on the size of the fistula, it can be accompanied by proptosis, chemosis, arterialization of conjunctival blood vessels, and cranial bruits [64]. Risks for development of fistula formation include head trauma, aneurysm and aneurysmal rupture, and connective tissue diseases like Ehlers–Danlos syndrome. Neurosurgical intervention with coil embolization is the recommended treatment and may assist in alleviating the accompanying headache [65] (Fig. 4a).

Arteriovenous Malformation

Chronic headache can occur in up to 15 % of patients diagnosed with arteriovenous malformations (AVM), which are abnormal communications between intracerebral arteries and veins with the absence of an intervening capillary system. This is a high-flow vascular malformation that can increase in size over time. There are feeding or

parent vessels that may become enlarged in addition to arterialized draining veins that may become dolichoectatic. Because of the high degree of flow, owing to the absence of intervening higher resistance vessels, AVMs may produce a shunt, siphoning blood away from the surrounding tissue, leading to calcific ischemic changes. Additionally, AVMs can cause mass effect, seizures, and focal neurological deficits and can lead to death, with a combined rate of morbidity or mortality estimated at 3 % per year [66, 67] (Fig. 4c–e). The headache accompanying AVM can mimic that of a primary headache with features of migraine [68], cluster, and TCH. In case studies, these headaches may respond to nonsteroidal anti-inflammatory medications and triptans. Furthermore, if located near the primary visual cortex, they can cause local irritation and possibly focal seizures that mimic visual aura [69, 70]. There is still debate about whether surgical intervention supersedes medical therapy in reducing the risk of morbidity and mortality associated with AVM [71]. Furthermore, the risks of surgical intervention must be balanced by the location and size of the AVM, with massive AVMs sometimes presenting too great a risk for catheter-based endovascular intervention using onyx embolization. Other treatment modalities include radiosurgery [72]. Patients with known AVM and migraine-like headaches presenting with an escalating, severe headache or TCH, should raise suspicion for intracranial hemorrhage. Since aneurysm formation can occur with AVM, aneurysmal rupture and SAH can complicate this disease.

Stroke-Related Headache

Headache has long been associated with hemorrhagic stroke and may be the result of extremes of hypertension in addition to the irritation of blood and vascular inflammation associated with intracranial hemorrhage. Other factors like release of matrix metalloproteinases and parenchymal inflammatory substances can cause irritation of the brain and its coverings, potentially precipitating the headache associated with hemorrhagic stroke. Additionally, ischemic stroke can have sentinel, early-onset (within the first few days of the stroke), or late-onset headaches. It is unclear if the timing of headache relates to differing pathobiological mechanisms. While headache that accompanies ischemic stroke may be an ominous sign of hemorrhagic conversion or increased brain edema, one study found similar functional 6-month outcomes in lacunar stroke patients with or without headache [73]. In a study examining 2196 ischemic stroke patients, 27 % presented with headache as part of their initial complaint. The frequency of headache at the onset of stroke varies considerably, with published estimates ranging between 7 and 65 %. This variability might reflect population-based differences in age, pathogenesis, and vascular distribution of stroke. Although the median age of stroke patients presenting with headache was slightly lower than stroke patients who did not have a headache, the median age for both populations was greater than 50 years, with interquartile ranges between 53 and 78 years of age. These data suggest that headache accompanying acute ischemic stroke is not restricted to younger migraineurs [11]. The headache can occur on the side of the artery involved in the acute ischemic stroke and has been described as throbbing in nature with moderate intensity [56]. The late-onset post-stroke headache is particularly intriguing and could be due to central post-stroke pain (CPSP) sensitization. Hansen et al. found that at 6 months following stroke, up to 13 % of patients who had newly diagnosed headache in the acute stroke phase had persistent headache. It may therefore be reasonable to start a preventive headache regimen for patients with persistent headache despite abortive therapies [74].

If there is co-occurring hypertension or cardiomyopathy, beta blockers, ACE inhibitors, or calcium channel blockers may be theoretically beneficial. Post-stroke depression is not uncommon. Therefore, in patients with post-stroke headache and depression, an antidepressant can serve a dual purpose of improving mood and preventing headaches.

Hypertensive Syndromes

Extremes of high blood pressure can cause significant disturbances in cerebral autoregulation, resulting in hypertensive encephalopathy and, over the course of years, lipohyalinotic change of small penetrating arteries leading to hemorrhagic stroke involving the deep brain nuclei. In addition to these phenomena, excessive hypertension can cause posterior reversible leukoencephalopathy.

Posterior Reversible Leukoencephalopathy Syndrome

Posterior reversible leukoencephalopathy syndrome (PRES) results from derangements in cerebral autoregulation with a predilection for the posterior circulation, possibly owing to differences in sympathetic innervation. Four to 53 % of patients with PRES present with headache. Other accompanying features include altered mental status, seizures, and vision loss. While hypertension is a well-recognized cause of PRES, PRES can follow administration of immunosuppressive agents like tacrolimus or cyclosporine, renal and liver failure, autoimmune diseases like lupus, and bone marrow transplantation. PRES is usually reversible, particularly when the underlying cause is rapidly identified and corrected and offending agents are withdrawn. In the case of hypertension, reducing the mean arterial pressure may require the use of nicardipine infusions, beta blockers,

and ACE inhibitors. Anticonvulsants should be used to help control seizures. The headache typically follows the course of the disease and remits after the underlying cause is addressed [75].

Intracranial Infection

Meningitis

Headache can accompany meningitis and occurs with varying combinations of fever, altered mental status, neck stiffness, and can be a complication of intracranial intervention or cranial trauma. In cases of suspected bacterial meningitis, the disease can be fulminant, progressing rapidly with neurological decline and death. Prompt examination of CSF is recommended in such cases. If the spinal fluid cannot be rapidly or safely obtained, it is prudent to initiate empirical antibiotic therapy before the CSF study. The headache associated with meningitis can improve with treatment of the underlying pathogen. Additional use of nonsteroidal anti-inflammatory agents may be beneficial [76, 77].

Cavernous Sinus Infection

Cavernous sinus infection is an uncommon disease but is associated with significant morbidity. Infection can occur in select patient populations and as an extension of other cranial sinusitis. Extension of nasopharyngeal abscess, skull-based fracture, and septic embolic events can also precipitate a cavernous sinusitis. Cavernous sinus infection can invade the cavernous internal carotid artery, leading to stroke and thrombosis (Fig. 5c–e). Biopsy of the lesion may be necessary for diagnosis and if invasive fungal rhinosinusitis is identified, treatment with antifungal agents may be lifesaving [78, 79]. Headache treatment may include opiate analgesics and nonsteroidal anti-inflammatory medications.

Postoperative and Postprocedural Headache

Patients can experience moderate to severe pain 24–48 h after intracranial surgery. In addition to acute headache following neurosurgery, 11 % of patients who have undergone supratentorial surgical procedures and 30 % who have undergone posterior fossa surgeries will continue to experience headache disorders 1 year later. However, whether aggressive perioperative analgesia reduces, the incidence of long-term head pain remains unclear [80]. Headache may also be a symptom of postoperative complications. Ventriculitis and meningitis are not common occurrences, since the advent of antibiotic-coated extraventricular drains and bundle approaches that utilize antibiotic containing wafers. Additionally, antibiotics are often administered intravenously before and after surgical procedures. Patients with ventricular drains or those who develop meningismus, worsening headache, confusion, or fevers postprocedurally require vigilance with early CSF studies and treatment.

Raised intracranial pressure, tumor debulking, and craniectomy for malignant cerebral edema can lead to CSF leakage and low-pressure orthostatic thunderclap-like head, neck, cervical, and intrascapular pain [54]. Additionally, with large skull defects, patients can suffer sagging or sinking of the skin flap—the "syndrome of the trephined." This can lead to parenchymal shift, impediment of venous return, cortical changes, and brain herniation. Headaches accompanying the syndrome of the trephined can be orthostatic and associated with dizziness, tinnitus, fatigue, and altered sensorium. This syndrome is usually alleviated with cranioplasty [81]. Additionally, pneumocephalus postoperatively can cause headache with seizure, nausea, and dizziness and may be improved with oxygen administration [82].

Intracranial and extracranial vascular procedures can cause postprocedural pain in the absence of surgical complications. Ipsilateral headache has been described with carotid artery stenting and carotid angiography. Following revascularization with carotid endarterectomy or stenting procedures, patients can also develop cerebral hyperperfusion syndromes whose hallmark is headache and can also develop encephalopathy, intracranial hemorrhage, focal neurological deficits, and seizures which may be alleviated with blood pressure lowering [83, 84].

Headache Due to Exacerbation of Primary Headache, Metabolic Problems, or Medications

Additional causes for headache in the neuroICU include the postictal period, hypercapnia, hypoxia, caffeine, nicotine, narcotic withdrawal, hemodialysis, and changes in fluid balance. Additionally, patients with a pre-existing primary headache syndrome may experience re-emergence of their headache precipitated by hormonal-, stress-, sleep-, and nutrition-related alterations.

Headache Unique to Intubated Patients

Exacerbated cervical pain due to neurogenic or muscular/postural neck conditions is quite common in the ICU. Prolonged endotracheal intubation and nasal feeding tubes can also be associated with rhinosinusitis-induced headache. Retropharyngeal tendinitis and abscess should also be kept in mind, as these might present with nuchal rigidity.

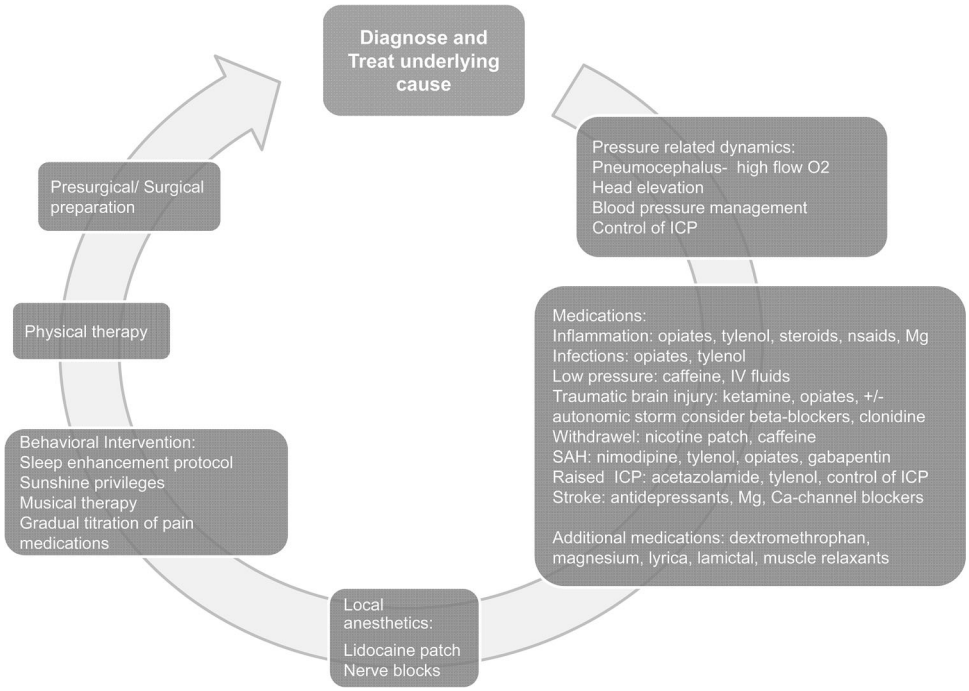

Fig. 6 Multimodal approach to headache management. When approaching headache in the neuroICU, first address diagnosing the type of headache and treating the offending agent or underlying cause. In the case of changes in intracranial pressure dynamics, changing the head position, controlling raised intracranial pressure and blood pressure may alleviate the headache. For additional disease-specific states, a broad range of medications can be administered. If there is focal pain, lidocaine patches or nerve blocks may be useful in limiting opiate analgesic use and sedating medications. Behavioral adjustments may increase comfort and decrease pain levels and agitation. Likewise, physical therapy can assist in decreasing pain related to immobility

Clinical Use of Opioid-Sparing Agents and Multimodal Approach to Treating Headache

While the primary pathology can vary from stroke to neck muscle spasms, the management of headache in the neuroICU is focused on treating the underlying cause by medical or surgical means and treating the headache symptoms. Traditionally, narcotics have been used to treat severe pain. Opiate analgesics have a role in the initial treatment of SAH, postsurgical, postoperative, and some post-stroke patients. To treat patients with refractory pain and to assist in liberating patients from chronic opiate analgesic use, initiation of medications like gabapentin may be useful. Likewise, for protracted headache following stroke, migraine-like headache preventive medications can be tried. Sedation, nausea, vomiting, pupillary miosis, decreased minute ventilation, and hypercapnia are feared adverse effects of opioids. Furthermore, hypercapnia can aggravate increases in cerebral blood flow and intracranial pressure. Individual dosing and the schedule and strength of each opioid can be found in standard textbooks. Nonsteroidal anti-inflammatory drugs tend to be avoided in patients with intracranial hemorrhage but may be useful in patients with vasculitis. Additional disease-specific medications like steroids or disease-modifying agents may be useful for secondary vasculitis-related headaches and calcium channel blockers for vasoconstriction syndrome. From presurgical planning to physical therapy, pain control plays a vital role in recovery and can be specifically targeted (Fig. 6). Perioperative local anesthetics can be helpful in reducing the need for postoperative pain medications. Avoiding use of short-acting opioids might avoid postoperative opioid-induced hyperalgesia [80]. Multiple opioid-sparing agents have been used to manage patients with headache in the ICU. While there is no proposed guideline tackling this topic, several studies demonstrate that opioid-sparing medications could be beneficial for headache. Intravenous acetaminophen can be safe and effective when used for perioperative pain in surgical ICU patients [80]. Oral gabapentin starting with 100 mg three times a day (tid) up to 900 mg tid is safe in SAH headache and may decrease the opioid requirement [18, 80]. Other antiepileptic medications like pregabalin [80] and carbamazepine [85] may improve central post-stroke pain (CPSP) syndrome and post-traumatic headache. Drug interaction, hyponatremia, and hepatotoxicity are common with these medications. Steroids could be very useful for postoperative pain

Table 1 Drugs and drug classes

Drugs/class	Dosage, administration	Indication/s	Side effects	Comments
Antiepileptics			Sedation, dizziness, fall	–
Gabapentin [18, 80, 85]	900–2700 mg/day po	SAH	Drug interaction	
		Headache/meningismus	Hyponatremia, Hepatotoxicity	
Pregabalin [80, 85]	150–300 mg /day po	CPSP	Skin reactions	
Carbamazepine [85]	600–1200 mg/day po	CPSP		
Phenytoin	300–400 mg/day po	CPSP		
Valproic acid [90]	800–1200 mg/day po	Post-traumatic headache		
Lamotrigine [85]	50–200 mg /day po	CPSP		
NSAIDS/ Acetaminophen		Postoperative, SAH	Hepatic toxicity	–
			Gastrointestinal bleed, decrease platelet function	
Acetaminophen [18, 80]	650–1000 mg / q6h po/iv			
Ketorolac [18, 80]	15–30 mg/q6h			
Diclofenac				
Parecoxib [80]	40 mg iv			
Antidepressant		CPSP, post-traumatic headache	Anticholinergic effects, serotonin syndrome	Avoid in case of RCVS
Amitriptyline [85, 90]	25–75 mg /day po			
Fluvoxamine [85]	50–125 mg/day po			
Calcium channel blocker		RCVS	Hypotension with higher iv dose	Higher iv dose more effective
				5–10 days of iv and 3–4 weeks of oral therapy
Nimodipine [91, 92]	100 mg tid po			
	30–60 mg q4h po			
	0.5–2 mg/h iv			
Nifedipine [91, 92]	20 mg tid po			
Corticosteroids			Hyperglycemia, hypertension, gastric mucosal damage, infection, adrenal suppression	–
Dexamethasone [18, 80]	2–4 mg/q8h	Postoperative/aseptic meningitis		
Methylprednisone [93]	1 gm iv 3 days	TA with threatened vision		
Prednisone [86]	45–60 mg/day po	TA, RCVS		
Others				
Magnesium [92]	1 g 20 %/h	RCVS		
Cabergoline/ bromocriptine [94]	–	Headache associated with pituitary diseases	Exacerbate headache	
Octreotide inj [94]	–	CPSP		
Baclofen [85]				
Local anesthetic block [92]	Intrathecal bupivacaine	Postoperative		
Propranolol [90]		Post-traumatic headache		Avoid in case of RCVS

CPSP Central post stoke pain, *RSCV* reversible segmental cerebral vasoconstriction, *TA* temporal arteritis, *SAH* subarachnoid hemorrhage, *PO* per oral, *iv* intravenous

management and aseptic meningitis [18]. Headache due to vasculitis can respond to steroids as well [86]. The complete list of medications, indications, proposed dosage, and side effects are listed in Table 1.

Role of Neuroimaging

The likelihood of finding a brain lesion on CT or MRI of the brain in patients presenting with an isolated headache in the

general population is low [87, 88]. However, in the critically ill population, the yield of imaging and re-imaging may be significantly higher [87]. Nonetheless, the clinical changes that should prompt re-imaging of headache patients in the neuroICU remain unclear. Many patients admitted to the NeuroICU will have repeat imaging for reasons other than worsening headache (to assess expansion of intracranial hemorrhage, cerebral edema, or worsened hydrocephalus). In the absence of these indications, when to re-imaging for headache will likely depend on the clinicians' degree of caution and suspicion for an underlying disease process whose discovery would warrant some medical or surgical intervention. Patients with worsening headache, escalating in intensity or frequency, or change in quality may require repeat brain imaging. For example, headache intensity that has been moderate for several days suddenly escalating to a maximal intensity headache could represent the initial signs of new hemorrhage, or re-hemorrhage following aneurysmal rupture, postsurgical resections, or stroke. Additionally, escalating headache could be a heralding symptom of raised intracranial pressure. Therefore, it may be prudent to re-image patients with known secondary headache syndromes if the headache dramatically worsens in intensity or requires more aggressive abortive therapies despite being previously controlled. New neurological deficits with worsening or refractory headache should prompt repeat imaging. In patients with head trauma, CT imaging may be indicated if they have depressed level of consciousness, worsened Glasgow coma scale score, new-onset seizure, or vomiting [89].

The issue of when to image in the postoperative setting can be challenging as well. Headache following surgical procedures is expected. However, headache with somnolence, worsened exam changes, or new exam findings should prompt a discussion about re-imaging. If the headache starts in the ICU, new-onset dull headache in the absence of exam change and without thunderclap-like symptoms is unlikely to reveal any radiographic pathology.

The need for re-imaging can present other challenges like transport of potentially unstable and intubated patients. CT scan may be the imaging modality of choice because it can be performed rapidly and gives information about not-so-subtle changes in the brain parenchyma. Additionally, portable CT scanners can mitigate the difficulty of patient transport and provide timely information about the cause of new or worsening headache.

Conclusion

Headache can accompany myriad neurological disease states in critically ill patients. Taken together with additional symptoms and clinical signs, the nature, location, duration, and escalation of headache can provide a helpful clue to the underlying diagnosis. While headaches are common in the critical care setting, they can precede major neurological decline and be the presenting feature of neurovascular complications. The ideal treatment for headache in this patient population depends heavily on the etiology of the headache syndrome and should focus on treating the underlying cause and being mindful of the potential deleterious effects of undertreating the headache and overtreating with opiate analgesics.

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Compliance with Ethical Standards

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