Headache and Brain Tumor

Shahram Hadidchi, MD[a], Wesley Surento, MS[a], Alexander Lerner, MD[a], Chia-Shang Jason Liu, MD, PhD[a], Wende N. Gibbs, MD, MA[a], Paul E. Kim, MD[a], Mark S. Shiroishi, MD, MS[b,*]

KEYWORDS

• Pediatric and adult brain tumor • Primary headache • Secondary headache
• Pathophysiology of brain tumor headache • Brain tumor treatment

KEY POINTS

- The majority headache patients will not have a brain tumor. However, the presence of clinical "red flags" should further investigation with neuroimaging.
- Brain tumors are an uncommon cause of headaches in children and adults, however, many brain tumors do present with headache, typically accompanied by other neurological signs and symptoms.
- Recent guidelines from the American College of Radiology are an excellent resource regarding the appropriate the use of neuroimaging for headaches in children and adults.

INTRODUCTION

Headaches are exceedingly common. A highly-cited general population prevalence study by Rasmussen and colleagues[1] found that the lifetime prevalence of headache in any form in the general population was 93% for men and 99% for women, with the point prevalence being 11% for men and 22% for women. Most headaches are primary headache disorders comprised mainly of tension (69%–88%), migraine (6%–25%), and cluster headaches (0.006%–0.24%).[1,2] Most individuals seeking medical attention for headaches have no serious or life-threatening underlying pathologies,[3] but many are concerned about this possibility.[4] A large case-control study[5] suggested that isolated headache presenting in the primary care setting did not justify further investigation, because the risk of an underlying brain tumor was too small. Likewise, the prevalence of asymptomatic brain tumors on neuroimaging studies is similarly low, estimated to be 0.7% (95% confidence interval [CI] 0.47%–0.98%) based on a meta-analysis of 16 studies (n = 19,559).[6]

The term atypical headache can be applied to those that are similar to primary headaches but have atypical features or clinical course. Although there are no definitive prevalence estimates of atypical headaches, one study found that major MR imaging abnormalities were found in 14.1% of atypical headache cases, while they were found in only 1.4% of tension-type and 0.6% of migraine headaches.[7] As opposed to primary headaches, the term secondary headaches refers to those with underlying pathologies such as intracranial tumor, infection, ruptured aneurysm, or giant cell arteritis. Secondary headaches are far less common than primary headaches.[8]

Admin Assistant: Kevin Pacheco. kevinpac@med.usc.edu.
M.S. Shiroishi was partially supported by NIH 1 L30 CA209248-01, Wright Foundation, American Cancer Society, Canon Medical Systems and the L. K. Whittier Foundation.
[a] Division of Neuroradiology, Department of Radiology, Keck School of Medicine, University of Southern California, 1520 San Pablo Street, Lower Level Imaging L1600, Los Angeles, CA 90033, USA; [b] Division of Neuroradiology, Department of Radiology, USC Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine of USC, University of Southern California, 1520 San Pablo Street, Lower Level Imaging L1600, Los Angeles, CA 90033, USA
* Corresponding author.
E-mail address: Mark.Shiroishi@med.usc.edu

Neuroimag Clin N Am 29 (2019) 291–300
https://doi.org/10.1016/j.nic.2019.01.008

This article describes the characteristics of headaches related to brain tumors in adults and children, provides neuroimaging recommendations in headache patients, and discusses the proposed pathophysiology and treatment of brain tumor-related headache.

HEADACHE IN ADULTS WITH BRAIN TUMORS

An underlying brain tumor is one of the most feared etiologies of headache, and, although brain tumors are an uncommon cause of headache,[9,10] many patients with brain tumors do complain of headaches.[10] The prevalence of headache in brain tumor patients ranges between 32.2% and 71% in unselected cases, and metastatic and primary brain tumors are equally likely to cause headaches.[11–16] Interestingly, there are anecdotal reports of patients with large intracranial tumors with increased intracranial pressure but no headache symptoms.[10] It is important to keep in mind that brain tumor-related headaches rarely present in isolation.[11,14,17] These headaches commonly present with other neurologic signs and symptoms like seizures, nausea/vomiting, personality changes, papilledema, blurred vision, and other focal neurologic deficits.[18,19] A change in the character of the headache, new symptoms, or progression are also concerning for an underlying brain tumor.[13]

The most recent International Classification of Headache Disroders-3[20] has defined "headache attributed to intracranial neoplasia" as one that occurs in a patient in whom an intracranial neoplasm has been diagnosed and in whom there is "evidence of causation demonstrated by one or more of the following: headache has developed in temporal relation to the intracranial neoplasia, or led to its discovery; headache has significantly worsened in parallel with worsening of the intracranial neoplasia; headache has significantly improved in temporal relation to successful treatment of the intracranial neoplasia; not better accounted for by another ICHD-3 diagnosis." The classic brain tumor headache has been described as severe, worse in the morning, and accompanied by nausea and vomiting.[12] An early clinical study of adult brain tumor headache was by Forsyth and Posner[12] in 1993 from Memorial Sloan-Kettering Cancer Center. They evaluated 111 consecutive brain tumor patients of whom 34% had primary brain tumors, and 66% had metastatic tumors. They found that 48% of primary and metastatic brain tumor patients presented with headaches and that the classic brain tumor headache was actually uncommon in their experience. Headaches were similar to tension-type in 77% of cases, migraine in 9% of cases, and other types in 14% of cases. However, unlike actual tension-type headaches, brain tumor headaches were worse with bending over in 32% of cases, while vomiting was seen 40% of the time. The headaches similar to tension-type headaches were described as dull ache, pressure, and like a sinus headache. Furthermore, larger tumors with contrast enhancement and midline shift were more likely to produce headaches, although the headache characteristics were nonspecific. The headaches were usually described as bilateral, but in those who had unilateral pain, the pain was always on the same side as the brain tumor. This finding was confirmed on a subsequent study from Thailand that found that this was highly predictive in both supra- and infratentorial tumors when there was no evidence of raised intracranial pressure.[15] In cases where intracranial pressure is elevated, tumor localization based on headache location becomes more difficult, likely because of widespread activation of pain receptors of the head.[10] Work from the early 1970s using electrical stimulation to the dura seemed to indicate that pain can be felt throughout the head and neck region.[21] This supports the general notion that determining tumor location based on headache distribution is imperfect, and with the availability of modern neuroimaging, this question can be easily answered.[10]

A 2007 study by Schankin and colleagues[14] of 85 patients with primary and metastatic tumors found that a pre-existing primary headache disorder could predispose to having a secondary brain tumor-related headache. The authors also suggested that an absence of raised intracranial pressure (such as could be seen after steroid treatment) could be responsible for the absence of classic brain tumor findings. They also suggested that glioblastoma patients had more dull headaches, while those with meningioma had pulsating headaches. An important prospective study by Valentinis and colleagues[16] in 2010 in 206 patients found that brain tumor headache prevalence was 47.6% and that the headache was nonspecific in character and that its prevalence differed according to tumor location, volume, and the patient's prior headache history. Like other studies,[13,15] they also found that infratentorial tumors were more commonly associated with headaches, likely because of the small size of the posterior fossa and CSF flow obstruction.[19]

Brain metastases are by far the most common brain tumors in adults, and in adults with a cancer history, a new or changed headache without other neurologic signs or symptoms can be associated with brain metastases in up to

54% of patients.[18,22] In children with a cancer history and new headache, the risk of intracranial metastatic diseases has been reported to be 12%.[23]

SELECTED BRAIN TUMOR HEADACHE SYNDROMES

Although a tumor's type, location, and size may not be predictably related to headache, there are some characteristic headache syndromes that appear to be associated with tumor location.[24,25]

Metastatic tumors to the skull base can elicit distinct clinical syndromes related to their location:[19,26]

- Orbital: dull unilateral supraorbital headache, diplopia, ptosis, V1 distribution trigeminal sensory loss
- Parasellar: unilateral frontal headache, V1 distribution sensory loss, diplopia, and ocular paresis
- Occipital condyle: severe unilateral occipital pain worsened with neck flexion and unilateral tongue paralysis
- Jugular foramen: unilateral retroauricular pain, IX to XI cranial nerve paralysis, hoarseness, and dysphagia
- Gasserian ganglion syndrome: trigeminal neural-like pain in forehead, cheek or jaw, and V2 or V3 distribution sensory loss

Trigeminal autonomic cephalgias (TACs) are primary headache syndromes comprised of severe short-lasting headaches along with paroxysmal facial autonomic symptoms.[27] Pituitary tumors have an unusual association with TACs, and so those presenting with this uncommon headache disorder should be considered for further work-up.[25] In an another context related to the pituitary gland, pituitary apoplexy is a well-known severe consequence of infarction/hemorrhage of a pituitary tumor. This is classically associated with acute severe headache, sometimes characterized as thunderclap, along with focal neurologic deficits including visual loss and potentially death from pituitary insufficiency.[28–33] Urgent surgery and glucocorticoid therapy are important to avoid serious complications; however, those with asymptomatic apoplexy may have good outcomes with tumor-specific and steroid treatments.[33,34]

Several cystic intracranial masses merit discussion. Colloid cysts classically produce severe acute headaches relieved by positional changes,[35] although more recent studies suggest that they more commonly cause intermittent diffuse headaches, often unrelated to position.[36] Acute obstruction at the foramen of Monro can be associated with severe consequences including death due to hydrocephalus.[28] Other cystic intracranial lesions such as anteroinferior middle cranial fossa arachnoid cysts may produce a nummular headache (left temporal headache location).[37] Supra- and intrasellar arachnoid cysts may produce unilateral cluster headache,[38] and large right frontal arachnoid cysts without hydrocephalus can produce occipital orgasmic headache.[39] When pineal cysts grow large enough to produce hydrocephalus, they may produce headache; however, it is theorized that those that are too small to result in hydrocephalus may still produce headache. After pinealectomy, these patients may still complain of unilateral headache with or without autonomic features and visual symptoms.[40] Melatonin is thought to have anti-inflammatory properties, and it is thought that tumors that infiltrate the pineal gland like germinoma can result in a decrease in melatonin, while other tumors like pinealoblastoma and pinealocytoma may actually increase levels of melatonin.[41] Other intracranial masses such as dermoid/epidermoid tumors and craniopharyngiomas may produce headache secondary to a chemical meningitis secondary to a rupture of their contents into the CSF.[37–39]

NEUROIMAGING RECOMMENDATIONS IN ADULTS WITH HEADACHE

Evaluation of the adult headache patient begins with a thorough history and physical examination. A useful resource regarding the use of neuroimaging in a headache patient is the American College of Radiology (ACR) Appropriateness Criteria Headache,[42] which provides evidence-based guidelines for physicians. The ACR recommends that most patients who present with nontraumatic, uncomplicated primary headache do not need neuroimaging. However, those who present with concerning red flags based on history or physical examination should be considered for neuroimaging to exclude an underlying secondary cause like a brain tumor. It is important for the physician to consider other serious intracranial disorders that could result in headache.[25] These are outlined in **Box 1**.

For patients with chronic headache, the ACR recommends that new headache features and/or focal neurologic signs/symptoms could suggest an underlying brain tumor, aneurysm, or vascular malformation, and in these cases contrast-enhanced brain MR imaging should be

Box 1
Differential diagnoses to consider other than brain tumor in a headache patient

- Other space-occupying processes (eg, hematoma or abscess)
- Subarachnoid hemorrhage
- Infection including encephalitis, meningitis
- Traumatic head injury
- Serious otolaryngologic and ophthalmologic causes of headache
- Stroke (intracerebral hemorrhage, infarction, cerebral venous thrombosis)
- Temporal arteritis

considered.[42] Other situations where neuroimaging may be indicated is with new headache in immunosuppressed or cancer patients because of the increased risk of infection or brain tumor. Various publications have proposed clinical red flags that should raise the suspicion of a serious underlying cause including brain tumor.[10,25,43] These are summarized in **Box 2**.

HEADACHE IN CHILDREN WITH BRAIN TUMORS

Brain tumors are the most common solid tumors of childhood and the leading cause of cancer death from ages 0 to 14 years in the United States.[44,45] The clinical presentation of pediatric brain tumors has been less studied than in adults.[46] Children with brain tumors frequently present with headaches, although their presentation may be less clear or complete relative to adults.[47] Brain tumor headaches in children, as in adults, are often associated with other neurologic signs and symptoms[14] (**Box 1**). Early diagnosis is critical to improving outcomes, but pediatric brain tumors are often initially misdiagnosed as more common pediatric disorders like migraine, gastroenteritis, or psychological/behavioral conditions.[48] Similarly, given the lack of pathognomonic clinical features of brain tumors in children, there has been no significant change in the prediagnostic interval in the last several decades despite widespread availability of computed tomography (CT) and MR imaging.

A large series[46] of 200 children with brain tumors found that the most common initial presenting symptoms were headache (41%), vomiting (12%), unsteadiness (11%), visual difficulties (10%), educational/behavioral problems (10%) and seizures (9%). The most common symptoms

Box 2
Clinical red flags warranting further evaluation with neuroimaging

- Headaches that occur immediately after waking at night or awaken patient repeatedly from sleep
- Headache with new neurologic signs
- Headache that is progressive
- Acute headache or persistent headache without associated family history of migraine
- Acute new, usually severe, headache or headache that has changed from prior headaches
- Acute headache following strenuous exercise
- Headache associated with fever or other systemic symptoms
- Headache with meningismus
- Headache with Valsalva maneuver (by bending down, coughing, sneezing, or straining)
- New headache in an adult, especially over 50 years of age
- New headache in the elderly or children
- Headaches not characteristic of primary headaches
- Headaches associated with vomiting/nausea without migraine
- Blurred vision, diplopia, papilledema
- New or changed headache in a cancer patient
- Chronic headaches occurring with substantial disorientation, confusion, or emesis
- Unilateral headache associated with contralateral neurologic symptoms
- Focal neurologic symptoms other than sensory or visual aura

occurring at any time were headache (56%), vomiting (51%), and educational or behavioral problems (44%). Eighty-eight percent of subjects had neurologic signs at diagnosis including papilledema (38%), cranial nerve abnormalities (49%), cerebellar signs (48%), long tract signs (27%), somatosensory abnormalities (11%), and reduced level of consciousness (12%). More than 1 sign or symptom was present at the time of diagnosis except for seizures. Other older large series also found that children with brain tumors typically have other neurologic signs and symptoms in addition to headache.[49,50] A recent review has summarized common physical examination findings in pediatric brain tumor patients (**Box 3**).[48]

Despite the fact that brain tumors are the most common solid tumors of childhood, only rarely

Box 3
Common physical examination findings in children with brain tumors

Cranial Nerves
- Nystagmus
- Facial palsy
- Double vision
- Reduced hearing
- Abnormal eye movement
- Difficulty swallowing
- Head tilt
- Deviation of tongue

Others
- Paresis
- Hyper/o reflexia
- Increased/decreased muscle tone
- Positive Romberg sign
- Dysmetria
- Heel-knee-shin ataxia
- Papilledema
- Clonus

will a child with a headache actually have a brain tumor. In a series of 105 children younger than 6 years with chronic and recurrent headaches, Raieli and colleagues[51] found only 3 (2.85%) cases with brain tumors. Another series of 104 children younger than 7 years with headache, the most common reason was migraine, and no brain tumor was found in their patients.[52] In a large series of 815 children younger than 18 years with chronic headache, Abu-Arafeh and Macleod[53] reported only 2 patients with brain tumors. A relatively recent series of 51 children with craniopharyngioma found that 78% of their subjects reported headache and that this was associated with hydrocephalus, distortion of circle of Willis, and large tumor volume.[54] Both distortion of the circle of Willis and large tumor volume were also associated with greater frequency and severity of headaches.

NEUROIMAGING RECOMMENDATIONS IN CHILDREN WITH HEADACHE

Although an actual underlying brain tumor is rare in a child, headaches can understandably result in enough concern from a clinician or parent to warrant neuroimaging.[55,56] As with adults, a thorough history and physical examination are vital in order to elicit whether red flags (see **Box 1**) are present. As with adults, the ACR recently published its evidenced-based guidelines regarding neuroimaging of children with headaches.[56]

The most common types of headache in children are primary headaches such as migraine or tension headaches. However, pediatric migraine headaches may differ from those in adults (eg, they may be of shorter duration in children).[57,58] The neuroimaging yield of clinically significant findings in pediatric patients with primary headaches is low.[55,59–63] Younger children are more likely to have secondary headaches, and while most have a benign cause, chronic progressive headaches, along with abnormal physical examination findings, could indicate an underlying brain tumor.[51,64] Imaging should be considered in those with nonspecific symptoms and normal physical examination results if there is not typical resolution of symptoms.[48] Urgent imaging should be particularly considered in those with paresis and unsteadiness. A summary of general guidelines for neuroimaging of headache that incorporates the ACR guidelines,[42,56] the American Academy of Neurology and Child Neurology Society,[65] and systematic review of neuroimaging in childhood headache[55] are summarized in **Box 4**.

Box 4
Recommendations for neuroimaging in children with headache

- Neuroimaging is usually not appropriate for the initial imaging of primary headache in children.
- In cases of secondary headache, noncontrast-enhanced brain MR imaging is usually appropriate, and a contrast-enhanced examination should be obtained if the noncontrast examination is abnormal.
- There are tradeoffs regarding the use of CT versus MR imaging in the neuroimaging of children. Children are exposed ionizing radiation with CT, while sedation or general anesthesia is sometimes needed for MR imaging examinations in children younger than 6 years. Given this, careful consideration is needed, and neuroimaging should be conducted in only those children with suspicious history and physical examination findings that point to serious intracranial pathology.
- If brain MR imaging reveals a brain tumor in a child, a contrast-enhanced MR imaging of the entire spine to exclude drop metastasis should be considered, especially for tumors of the posterior fossa.

PATHOPHYSIOLOGY OF HEADACHE IN BRAIN TUMORS

The brain parenchyma itself is insensitive to pain because it lacks pain receptors. However, the tissues covering the cranium, including the periosteum of the skull, muscles, vessels, skin/subcutaneous tissues; eye, ear paranasal sinuses, and nasal cavity; dural venous sinuses; pia arachnoid and dura mater; trigeminal, glossopharyngeal, vagus, and first 3 cervical nerves are sensitive to mechanical stimulation.[17] It is generally thought that displacement and traction of these sensitive intracranial structures underlie brain tumor-related headaches. Raised intracranial pressure results in traction due to brain tumor edema, tumor expansion, and hemorrhage.[66] The clinicoradiologic correlates of increased intracranial pressure including midline shift, papilledema, and peritumoral edema are typically associated with poorly localized diffuse headaches.[12,13] However, this relationship is imperfectly understood, and further work, including that focusing on serologic, cerebral, and CSF factors is needed to better define the pathophysiology.[10]

Brain tumor headaches can sometimes be intense but temporary because of transitory ventricular system obstruction from the tumor induced by exertion, postural change, Valsalva maneuver, and coughing.[10] An abnormal cerebrovascular autoregulatory response to vasodilation related to raised intracranial pressure and/or space-occupying event is another postulated mechanism of acute brain tumor headaches.[10]

The growth rate of brain tumors can also influence the characteristics of headaches.[13,19,66] Because slow-growing tumors can allow adaptation to mass effect, they can produce transitory headaches later in the disease process. On the other hand, fast-growing tumors do not allow adaptation and so can result in intense, sharp pain.

Brain tumor location may also impact whether a headache is produced. Brain tumors that are midline, intraventricular, and posterior fossa in location are generally known to result in headaches due to CSF flow obstruction.[11,13,15,66] Although cranial nerves and cervical nerve roots are sensitive to pain, nerve compression itself is rarely thought to result in brain tumor headache.[11] However, when cervical nerve compression appears to be associated with brain tumor headache, it can be seen along with the presence of myofascial trigger points and muscle tenderness, likely triggered by external pressure or neck movements.[10]

In certain situations, little or no direct mass effect on pain-sensitive structures from tumors might result in brain tumor headaches. This is thought to be due to endocrinological etiologies, such as with pituitary tumors where somatostatin and dopamine may have a potential proprioceptive role in the development of headache.[67,68] Other publications posit that pituitary tumors cause headaches because of a cavernous sinus invasion and dural stretching.[69] Other possible causes of brain tumor headaches include substances produced by brain tumors such as tachykinin (substance P), calcitonin gene-related peptide, nitric oxide synthase, tumor necrosis factor alpha, and vasoactive intestinal peptide.[24]

Finally, the treatment of brain tumors itself can result in headache, and these factors are summarized in **Box 5**.[70] Several surgical series have reported a high incidence of postcraniotomy headache, both immediately and remote,[71–75] especially in the case of retrosigmoid craniotomy.[76] Radiation therapy of the brain can result in immediate or remote headache and can be associated with worsening of neurologic function.[77] Cerebral radiation necrosis can occur months to years after initial treatment and can be associated with focal neurologic deficits and headache.[25] In high-grade glioma patients treated with temozolomide chemoradiation, increased edema and contrast-enhancement immediately after treatment can worsen symptoms and result in headaches.[78] Temozolomide itself has also been associated with headache in glioblastoma patients.[79] Other agents used in the treatment of brain tumors such as corticosteroids and antinausea agents like ondansetron[80] and bevacizumab[81] are also known to result in headaches.

TREATMENT OF BRAIN TUMOR HEADACHES

For brain tumor patients with headache, treatment of the underlying neoplasm improves the headache in most cases.[13,16,82,83] Because patients

Box 5
Brain tumor treatment factors associated with headache

- Craniotomy
- Radiation therapy – both acute and remote, including radiation necrosis
- Chemotherapy agents (eg, temozolomide)
- Corticosteroids
- Bevacizumab
- Antinausea agents (eg, ondansetron)

with a history of a primary headache disorder more commonly suffer from brain tumor-related headaches,[12,16] if a headache appears to be primary, rather than secondary in a brain tumor patient, conventional therapy for the primary headache is warranted.[25] Medical therapy with analgesics and opiates is commonly used,[24,25] and in cases with highly aggressive brain malignancies, adequate pain control is central to quality of life. Control of hydrocephalus with intracranial pressure monitoring and ventricular shunting and management of cerebral edema are key initial treatment strategies before chemotherapy, radiotherapy, or surgical therapy.[24] Corticosteroid treatment for cerebral edema can result in substantial transient improvement of headache. In patients with cerebral metastases, whole-brain radiation may improve headache symptoms and decrease corticosteroid usage.[84,85] Surgical resection or stereotactic radiosurgery for those with a few metastases can also result in control of headache.[86–88]

SUMMARY

Most headache patients will not have life-threatening illnesses like a brain tumor. However, the clinician must perform a careful history and physical examination for the presence of red flags that would warrant neuroimaging. Brain tumors are an uncommon cause of headaches in children and adults; however, many brain tumors do present with headache, typically accompanied by other neurologic signs and symptoms. Early diagnosis of pediatric brain tumors remains especially difficult, because they can be initially misdiagnosed as more common benign disorders. Generally, the treatment of the underlying brain tumor improves the headache; however, these therapies may also induce headaches. The recent evidence-based guidelines from the ACR[42,56] serve as an excellent resource for clinicians regarding the use neuroimaging for headaches in children and adults.

REFERENCES

1. Rasmussen BK, Jensen R, Schroll M, et al. Epidemiology of headache in a general population–a prevalence study. J Clin Epidemiol 1991;44(11):1147–57.
2. Dousset V, Henry P, Michel P. Epidemiology of headache. Rev Neurol (Paris) 2000;156(Suppl 4):4S24–9 [in French].
3. Kernick D, Stapley S, Goadsby PJ, et al. What happens to new-onset headache presented to primary care? A case-cohort study using electronic primary care records. Cephalalgia 2008;28(11):1188–95.
4. Kurth T, Buring JE, Rist PM. Headache, migraine and risk of brain tumors in women: prospective cohort study. J Headache Pain 2015;16:501.
5. Hamilton W, Kernick D. Clinical features of primary brain tumours: a case-control study using electronic primary care records. Br J Gen Pract 2007;57(542):695–9.
6. Morris Z, Whiteley WN, Longstreth WT Jr, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ 2009;339:b3016.
7. Wang HZ, Simonson TM, Greco WR, et al. Brain MR imaging in the evaluation of chronic headache in patients without other neurologic symptoms. Acad Radiol 2001;8(5):405–8.
8. Frishberg BM, Rosenberg JH, Matchar DB, et al. Evidence-based guidelines in the primary care setting: neuroimaging in patients with nonacute headache 2000. Available at: tools.aan.com/professionals/practice/pdfs/gl0088.pdf.
9. Taylor LP. Mechanism of brain tumor headache. Headache 2014;54(4):772–5.
10. Goffaux P, Fortin D. Brain tumor headaches: from bedside to bench. Neurosurgery 2010;67(2):459–66.
11. Vazquez-Barquero A, Ibanez FJ, Herrera S, et al. Isolated headache as the presenting clinical manifestation of intracranial tumors: a prospective study. Cephalalgia 1994;14(4):270–2.
12. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. Neurology 1993;43(9):1678–83.
13. Pfund Z, Szapary L, Jaszberenyi O, et al. Headache in intracranial tumors. Cephalalgia 1999;19(9):787–90 [discussion: 765].
14. Schankin CJ, Ferrari U, Reinisch VM, et al. Characteristics of brain tumour-associated headache. Cephalalgia 2007;27(8):904–11.
15. Suwanwela N, Phanthumchinda K, Kaoropthum S. Headache in brain tumor: a cross-sectional study. Headache 1994;34(7):435–8.
16. Valentinis L, Tuniz F, Valent F, et al. Headache attributed to intracranial tumours: a prospective cohort study. Cephalalgia 2010;30(4):389–98.
17. Boiardi A, Salmaggi A, Eoli M, et al. Headache in brain tumours: a symptom to reappraise critically. Neurol Sci 2004;25(Suppl 3):S143–7.
18. Christiaans MH, Kelder JC, Arnoldus EP, et al. Prediction of intracranial metastases in cancer patients with headache. Cancer 2002;94(7):2063–8.
19. Loghin M, Levin VA. Headache related to brain tumors. Curr Treat Options Neurol 2006;8(1):21–32.
20. Society TIH. The International classification of headache disorders. 3rd edition 2018. Available at: https://www.ichd-3.org/.

21. Wirth FP Jr, Van Buren JM. Referral of pain from dural stimulation in man. J Neurosurg 1971;34(5):630–42.
22. Argyriou AA, Chroni E, Polychronopoulos P, et al. Headache characteristics and brain metastases prediction in cancer patients. Eur J Cancer Care (Engl) 2006;15(1):90–5.
23. Antunes NL. The spectrum of neurologic disease in children with systemic cancer. Pediatr Neurol 2001;25(3):227–35.
24. Kahn K, Finkel A. It is a tumor – current review of headache and brain tumor. Curr Pain Headache Rep 2014;18(6):421.
25. Kirby S, Purdy RA. Headaches and brain tumors. Neurol Clin 2014;32(2):423–32.
26. Greenberg HS, Deck MD, Vikram B, et al. Metastasis to the base of the skull: clinical findings in 43 patients. Neurology 1981;31(5):530–7.
27. Favier I, van Vliet JA, Roon KI, et al. Trigeminal autonomic cephalgias due to structural lesions: a review of 31 cases. Arch Neurol 2007;64(1):25–31.
28. de Witt Hamer PC, Verstegen MJ, De Haan RJ, et al. High risk of acute deterioration in patients harboring symptomatic colloid cysts of the third ventricle. J Neurosurg 2002;96(6):1041–5.
29. Satoh H, Uozumi T, Arita K, et al. Spontaneous rupture of craniopharyngioma cysts. A report of five cases and review of the literature. Surg Neurol 1993;40(5):414–9.
30. Gormley WB, Tomecek FJ, Qureshi N, et al. Craniocerebral epidermoid and dermoid tumours: a review of 32 cases. Acta Neurochir (Wien) 1994;128(1–4):115–21.
31. Stendel R, Pietila TA, Lehmann K, et al. Ruptured intracranial dermoid cysts. Surg Neurol 2002;57(6):391–8 [discussion: 398].
32. Levy MJ, Jager HR, Powell M, et al. Pituitary volume and headache: size is not everything. Arch Neurol 2004;61(5):721–5.
33. Nawar RN, AbdelMannan D, Selman WR, et al. Pituitary tumor apoplexy: a review. J Intensive Care Med 2008;23(2):75–90.
34. Chen L, White WL, Spetzler RF, et al. A prospective study of nonfunctioning pituitary adenomas: presentation, management, and clinical outcome. J Neurooncol 2011;102(1):129–38.
35. Harris W. Paroxysmal and postural headaches from intraventricular cysts and tumors. Lancet 1944;2:654–5.
36. Desai KI, Nadkarni TD, Muzumdar DP, et al. Surgical management of colloid cyst of the third ventricle–a study of 105 cases. Surg Neurol 2002;57(5):295–302 [discussion: 302–4].
37. Guillem A, Barriga FJ, Gimenez-Roldan S. Nummular headache associated to arachnoid cysts. J Headache Pain 2009;10(3):215–7.
38. Edvardsson B, Persson S. Cluster headache and arachnoid cyst. Springerplus 2013;2(1):4.
39. Kang SY, Choi JC, Kang JH, et al. Huge supratentorial arachnoid cyst presenting as an orgasmic headache. Neurol Sci 2012;33(3):639–41.
40. Chazot G, Claustrat B, Broussolle E, et al. Headache and depression: recurrent symptoms in adult pinealectomized patients. In: Nappi G, Al E, editors. Headache and depression: serotonin pathways as a common clue. New York: Raven Press; 1991. p. 299–303.
41. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. Sleep Med Rev 2005;9(1):11–24.
42. Douglas AC, Wippold FJ 2nd, Broderick DF, et al. ACR appropriateness criteria headache. J Am Coll Radiol 2014;11(7):657–67.
43. Purdy RA. Clinical evaluation of a patient presenting with headache. Med Clin North Am 2001;85(4):847–63, v.
44. Linabery AM, Ross JA. Trends in childhood cancer incidence in the U.S. (1992-2004). Cancer 2008;112(2):416–32.
45. Ostrom QT, de Blank PM, Kruchko C, et al. Alex's Lemonade Stand Foundation infant and childhood primary brain and central nervous system tumors diagnosed in the United States in 2007-2011. Neuro Oncol 2015;16(Suppl 10):x1–36.
46. Wilne SH, Ferris RC, Nathwani A, et al. The presenting features of brain tumours: a review of 200 cases. Arch Dis Child 2006;91(6):502–6.
47. Punt J. Clinical syndromes. In: Walker D, Perilongo G, Punt J, editors. Brain and spinal tumours of childhood. London: Arnold; 2004. p. 99–106.
48. Goldman RD, Cheng S, Cochrane DD. Improving diagnosis of pediatric central nervous system tumours: aiming for early detection. CMAJ 2017;189(12):E459–63.
49. The epidemiology of headache among children with brain tumor. Headache in children with brain tumors. The Childhood Brain Tumor Consortium. J Neurooncol 1991;10(1):31–46.
50. Medina LS, Pinter JD, Zurakowski D, et al. Children with headache: clinical predictors of surgical space-occupying lesions and the role of neuroimaging. Radiology 1997;202(3):819–24.
51. Raieli V, Eliseo M, Pandolfi E, et al. Recurrent and chronic headaches in children below 6 years of age. J Headache Pain 2005;6(3):135–42.
52. Chu M, Shinnar S. Headaches in children younger than 7 years of age. Arch Neurol 1992;49(1):79–82.
53. Abu-Arafeh I, Macleod S. Serious neurological disorders in children with chronic headache. Arch Dis Child 2005;90(9):937–40.
54. Khan RB, Merchant TE, Boop FA, et al. Headaches in children with craniopharyngioma. J Child Neurol 2013;28(12):1622–5.

55. Alexiou GA, Argyropoulou MI. Neuroimaging in childhood headache: a systematic review. Pediatr Radiol 2013;43(7):777–84.
56. Expert Panel on Pediatric I, Hayes LL, Palasis S, et al. ACR appropriateness criteria((R)) headache-child. J Am Coll Radiol 2018;15(5S):S78–90.
57. Lateef TM, Grewal M, McClintock W, et al. Headache in young children in the emergency department: use of computed tomography. Pediatrics 2009;124(1): e12–7.
58. Arruda MA, Guidetti V, Galli F, et al. Primary headaches in childhood–a population-based study. Cephalalgia 2010;30(9):1056–64.
59. Schwedt TJ, Guo Y, Rothner AD. "Benign" imaging abnormalities in children and adolescents with headache. Headache 2006;46(3):387–98.
60. Sempere AP, Porta-Etessam J, Medrano V, et al. Neuroimaging in the evaluation of patients with non-acute headache. Cephalalgia 2005; 25(1):30–5.
61. DeVries A, Young PC, Wall E, et al. CT scan utilization patterns in pediatric patients with recurrent headache. Pediatrics 2013;132(1):e1–8.
62. Martens D, Oster I, Gottschlling S, et al. Cerebral MRI and EEG studies in the initial management of pediatric headaches. Swiss Med Wkly 2012;142: w13625.
63. Yilmaz U, Celegen M, Yilmaz TS, et al. Childhood headaches and brain magnetic resonance imaging findings. Eur J Paediatr Neurol 2014;18(2):163–70.
64. Nallasamy K, Singhi SC, Singhi P. Approach to headache in emergency department. Indian J Pediatr 2012;79(3):376–80.
65. Lewis DW, Ashwal S, Dahl G, et al. Practice parameter: evaluation of children and adolescents with recurrent headaches: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2002; 59(4):490–8.
66. Kunkle EC, Ray BS, Wolff HG. Studies on headache: the mechanisms and significance of the headache associated with brain tumor. Bull N Y Acad Med 1942;18(6):400–22.
67. Williams G, Ball JA, Lawson RA, et al. Analgesic effect of somatostatin analogue (octreotide) in headache associated with pituitary tumours. Br Med J (Clin Res Ed) 1987;295(6592):247–8.
68. Levy MJ, Matharu MS, Goadsby PJ. Prolactinomas, dopamine agonists and headache: two case reports. Eur J Neurol 2003;10(2):169–73.
69. Levy MJ. The association of pituitary tumors and headache. Curr Neurol Neurosci Rep 2011;11(2): 164–70.
70. Obermann M, Holle D, Naegel S, et al. Headache attributable to nonvascular intracranial disorders. Curr Pain Headache Rep 2011;15(4):314–23.
71. Rocha-Filho PA. Post-craniotomy headache: a clinical view with a focus on the persistent form. Headache 2015;55(5):733–8.
72. de Oliveira Ribeiro Mdo C, Pereira CU, Sallum AM, et al. Immediate post-craniotomy headache. Cephalalgia 2013;33(11):897–905.
73. Rocha-Filho PA, Fujarra FJ, Gherpelli JL, et al. The long-term effect of craniotomy on temporalis muscle function. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104(5):e17–21.
74. Ryzenman JM, Pensak ML, Tew JM Jr. Headache: a quality of life analysis in a cohort of 1,657 patients undergoing acoustic neuroma surgery, results from the acoustic neuroma association. Laryngoscope 2005;115(4):703–11.
75. Rimaaja T, Haanpaa M, Blomstedt G, et al. Headaches after acoustic neuroma surgery. Cephalalgia 2007;27(10):1128–35.
76. Ansari SF, Terry C, Cohen-Gadol AA. Surgery for vestibular schwannomas: a systematic review of complications by approach. Neurosurg Focus 2012;33(3):E14.
77. Schultheiss TE, Kun LE, Ang KK, et al. Radiation response of the central nervous system. Int J Radiat Oncol Biol Phys 1995;31(5):1093–112.
78. Brandsma D, Stalpers L, Taal W, et al. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol 2008;9(5):453–61.
79. Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. Br J Cancer 2000;83(5):588–93.
80. Kalaycio M, Mendez Z, Pohlman B, et al. Continuous-infusion granisetron compared to ondansetron for the prevention of nausea and vomiting after high-dose chemotherapy. J Cancer Res Clin Oncol 1998; 124(5):265–9.
81. Lou E, Turner S, Sumrall A, et al. Bevacizumab-induced reversible posterior leukoencephalopathy syndrome and successful retreatment in a patient with glioblastoma. J Clin Oncol 2011;29(28): e739–42.
82. Schmidinger M, Linzmayer L, Becherer A, et al. Psychometric- and quality-of-life assessment in long-term glioblastoma survivors. J Neurooncol 2003; 63(1):55–61.
83. Pace A, Di Lorenzo C, Guariglia L, et al. End of life issues in brain tumor patients. J Neurooncol 2009; 91(1):39–43.
84. Steinmann D, Paelecke-Habermann Y, Geinitz H, et al. Prospective evaluation of quality of life effects in patients undergoing palliative radiotherapy for brain metastases. BMC Cancer 2012; 12:283.
85. Wong J, Hird A, Zhang L, et al. Symptoms and quality of life in cancer patients with brain metastases

following palliative radiotherapy. Int J Radiat Oncol Biol Phys 2009;75(4):1125–31.
86. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990; 322(8):494–500.
87. Kondziolka D, Patel A, Lunsford LD, et al. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. Int J Radiat Oncol Biol Phys 1999;45(2):427–34.
88. Sanghavi SN, Miranpuri SS, Chappell R, et al. Radiosurgery for patients with brain metastases: a multi-institutional analysis, stratified by the RTOG recursive partitioning analysis method. Int J Radiat Oncol Biol Phys 2001;51(2):426–34.