Headache in Brain Tumors

Fawad A. Khan, MD

Director, The McCasland Family Comprehensive Headache Center

Ochsner Neuroscience Institute


GRAY OVER THE BAY
Ocean Springs, MS
Brain Cancer
Awareness Walk
May 13, 2023 • 9:00 AM
Biloxi/Ocean Springs Bay Bridge

Relevant financial conflicts of interest

- Advisory fees from Pfizer
- Speaker compensation from Amgen, Allergan, Lilly USA, Impel Pharmaceuticals, AbbVie
- Institutional research support from Amgen, Teva Pharmaceutical, Biohaven Pharmaceutical, Abbvie.
- All disclosures were outside the submitted work. , all outside of the submitted work.

Learning objectives

1. Recognizing headache in brain tumors
2. Understanding features of headache in brain tumors
3. Reviewing headache in select conditions -Pituitary Adenoma, Rathke Cleft Cyst, Craniopharyngioma
4. Understanding headache secondary to brain tumor treatment

Headache – Brain Tumor connection

- Headache occurs in nearly 50-60% of patients with a newly diagnosed brain tumor
  - Valentinis L, Tuniz F, Valent F, et al. Headache attributed to intracranial tumours: a prospective cohort study. Cephalalgia. 2010;30(4):389-398
  - Campbell JK, Caselli RJ. Headache and other craniofacial pain. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, editors. Neurology in clinical practice 1991:1507-48

- When Should a Headache Prompt Evaluation for Brain Tumor?

  Headaches with the following associated symptoms are concerning for the possibility of a brain tumor and warrant prompt evaluation. These symptoms include acute, severe headaches that represent a change from prior headache pattern, new headaches in older adults or children, headaches that are positional or worsen with exertion, and headaches associated with any new neurologic sympto


Clinical Review & Education

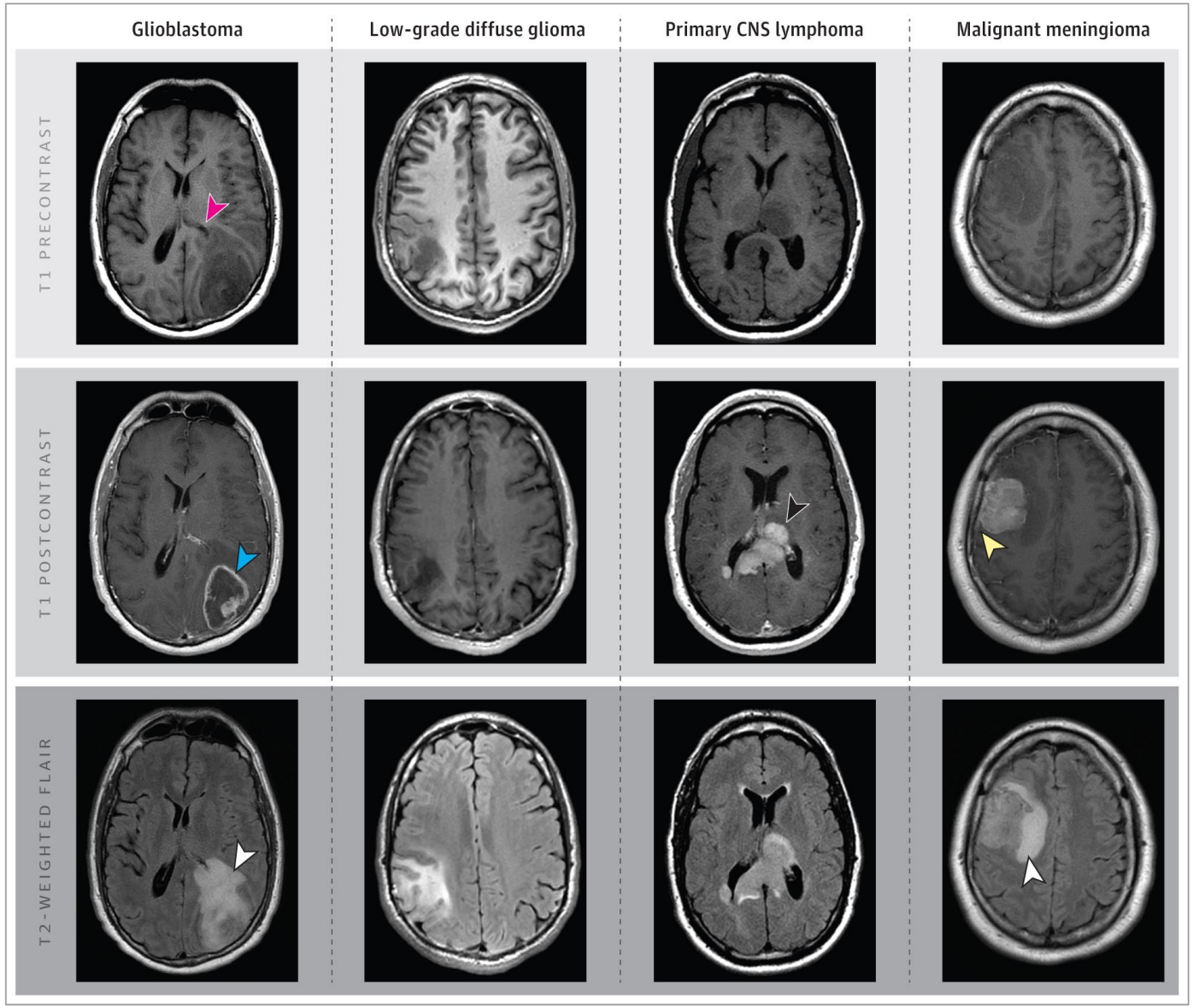
JAMA | Review

Glioblastoma and Other Primary Brain Malignancies in Adults
A Review

Lauren R. Schaff, MD; Ingo K. Mellinghoff, MD

From: **Glioblastoma and Other Primary Brain Malignancies in Adults: A Review**

JAMA. 2023;329(7):574-587. doi:10.1001/jama.2023.0023



Imaging in Headache

- Early diagnosis of brain tumors allows prompt treatment before more severe symptoms, reduced performance status, and worsened outcomes
- Brain tumors may present with isolated headaches
  - Vázquez-Barquero A, ,Ibáñez FJ, Herrera S, lzquierdo JM, Berciano J, Pascual J. Isolated headache as the presenting clinical manifestation of intracranial tumors: a prospective study. Cephalalgia 1994;1'4:270-1.
- Highest quality of care

- ❑ Prospective study (2 years)
- ❑ Incidence of headache as the initial and isolated clinical manifestation of adult patients suffering from intracranial tumors (n = 183).
- ❑ 8% exhibited headache as their first and isolated clinical manifestation.
- ❑ Age, sex, neoplasm localization, or pathological diagnosis did not correlate with the presence of headache

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Choosing Wisely®

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American College of Radiology

ACR® American College of Radiology

Quality is Our Image

Ten Things Physicians and Patients Should Question

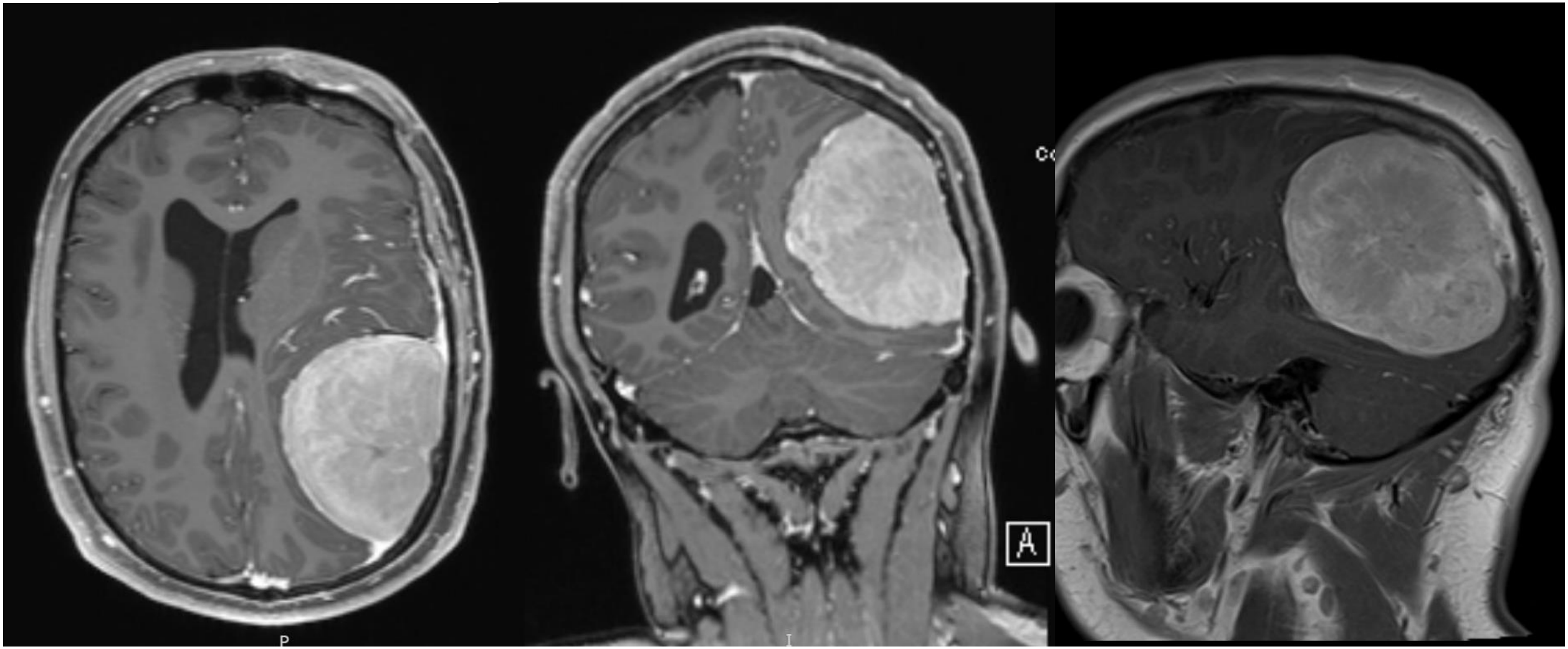
Don't do imaging for uncomplicated headache.

Imaging headache patients absent specific risk factors for structural disease is not likely to change management or improve outcome. Those patients with a significant likelihood of structural disease requiring immediate attention are detected by clinical screens that have been validated in many settings. Many studies and clinical practice guidelines concur. Also, incidental findings lead to additional medical procedures and expense that do not improve patient well-being.

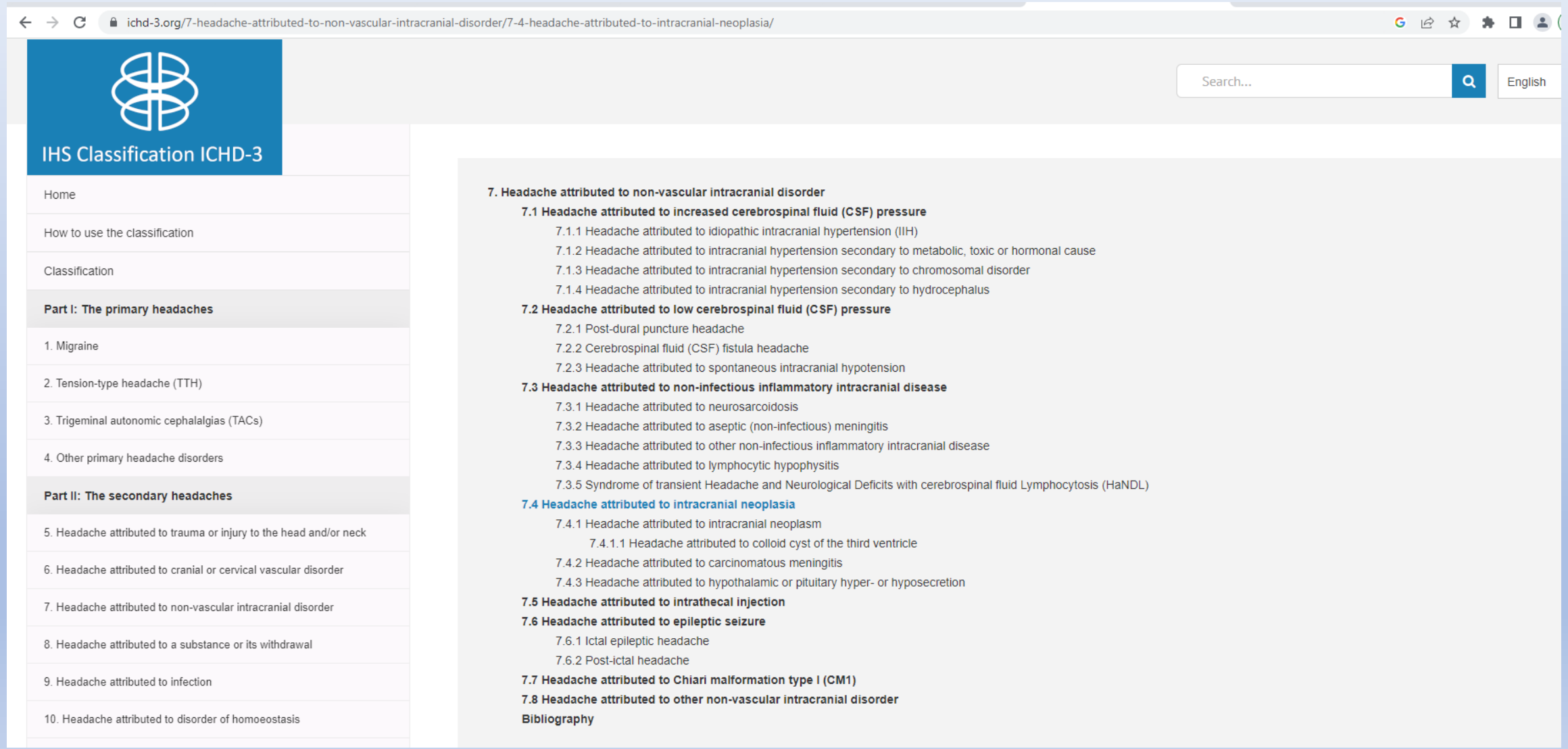
3-7% brain tumors would have never got imaged per guidelines or because looked like a migraine/tension headache

Hawasli, Ammar H. MD, PhD; Chicoine, Michael R. MD; Dacey, Ralph G. Jr MD. Choosing Wisely: A Neurosurgical Perspective on Neuroimaging for Headaches. Neurosurgery 76(1):p 1-6, January 2015.

Asymptomatic cases



Diagnosis of the Headache



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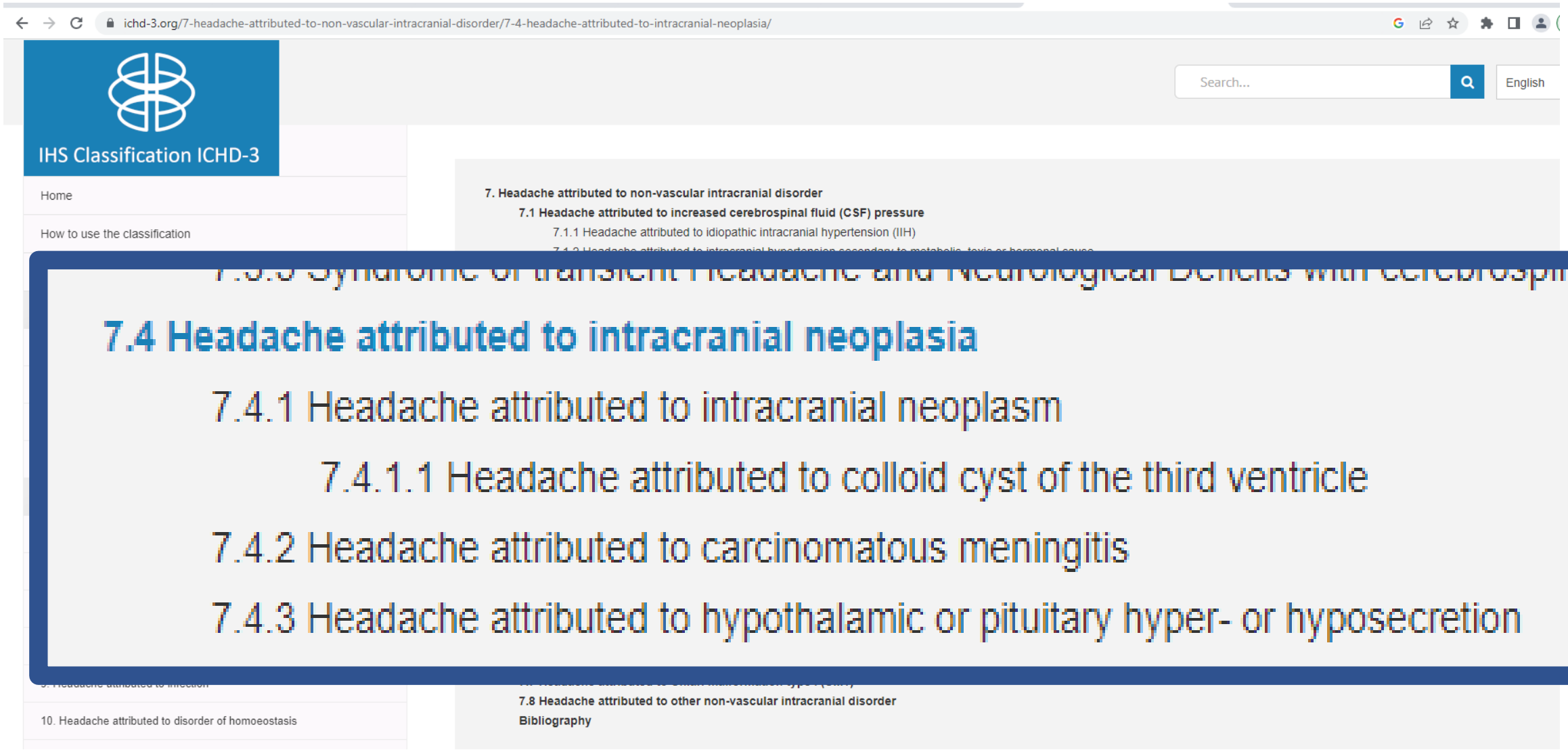

Diagnostic criteria

A. Headache fulfilling criterion C

B. A non-vascular intracranial disorder known to be able to cause headache has been diagnosed

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

- headache has developed in temporal relation to the onset of the non-vascular intracranial disorder, or has led to its discovery
- either or both of the following:
  - a) headache has significantly worsened in parallel with worsening of the non-vascular intracranial disorder
  - b) headache has significantly improved in parallel with improvement in the non-vascular intracranial disorder
  - headache has characteristics typical for the non-vascular intracranial disorder
- other evidence exists of causation

D. Not better accounted for by another ICHD-3 diagnosis.

Clinical presentations – Pediatrics

- Headache is most common presenting symptom
- Other symptoms - vomiting, unsteadiness, behavioral problems, and cranial nerve palsies, most commonly nocturnally or in the early morning
- Most common misdiagnosis - migraine
- Infratentorial tumors more likely than supratentorial tumors

Ullrich NJ. Neurologic sequelae of brain tumors in children. J Child Neurol. 2009;24:1446-1454.

Klitbo DM, Nielsen R, Illum NO, et al. Symptoms and time to diagnosis in children with brain tumours. Dan Med Bull. 2011;58:A4285.

Nature of Headache

- Headache associated with brain neoplasms has no unique clinical picture besides a similarity to tension-type headache in two-fifths of patients.
- The most important risk factor for developing headache while suffering from a brain tumor is having had a pre-existing headache.

  Schankin, C. J., et al. "Characteristics of brain tumour-associated headache." Cephalalgia 27.8 (2007): 904-911.
- A prospective study found no association between histopathological diagnoses and presence of headache

  Valentinis L, Tuniz F, Valent F. Headache attributed to intracranial tumors: A prospective cohort study. Cephalalgia. 2010;30:389-398.

- New onset
- Thunderclap
- Different from other headaches (most common is tension type, second is migraine)

  Valentinis L, Tuniz F, Valent F. Headache attributed to intracranial tumors: A prospective cohort study. Cephalalgia. 2010;30:389-398.
- Progressively severe headache in >79%

  Pfund Z, Szapary L, Jaszberenyi O, et al. Headache in intracranial tumors. Cephalalgia. 1999;19:787-790.
- Ipsilateral Location on skull in 30-80% of cases

  Loghin M, Levin VA. Headache related to brain tumors. Curr Treat Options Neurol. 2006;8:21-32.
- Posterior fossa location and hydrocephalus related headache
- Medulla compression

  Vilanilam, George K., et al. "Compressive lesions of the head and neck: Common and uncommon must-know entities." The Neuroradiology Journal (2023): 19714009231166083.
- CSF circulation - partially obstructed, headache: generalized and worse in the occipitonuchal area, improves on awakening, aggravated by coughing and straining, associated with nausea and vomiting.
- Intraventricular tumors, present dramatically with sudden, severe headache, rapidly accompanied by nausea and vomiting and progressing to loss of consciousness

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Secondary Trigeminal Autonomic Cephalalgias

Table –. Characteristics of Trigeminal Autonomic Cephalalgias

TAC Type	# Attacks	Pain Duration	Frequency	Restlessness	Indomethacin Sensitivity
Cluster	≥5	15 minutes-3 hours	1 qod-8/day	Present	Absent
Paroxysmal hemicranias	≥20	2-30 minutes	>5/day (>50% of the time)	Absent	Present
Hemicrania continua	N/A	>3 months with exacerbations	N/A	Present	Present
SUNCT	≥20	1 second-10 minutes	1/day (>50% of the time)	Absent	Absent

SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; qod = every other day.

Nelson, Sarah, and Lynne P. Taylor. "Headaches in brain tumor patients: primary or secondary?." *Headache: The Journal of Head and Face Pain* 54.4 (2014): 776-785.

Secondary Trigeminal Autonomic Cephalalgias

- Prolactinoma
- Acoustic neuroma
- Foramen magnum meningioma
- Posterior fossa tumors such as schwannomas and meningiomas

Loghin M, Levin VA. Headache related to brain tumors. Curr Treat Options Neurol. 2006;8:21-32.

Trucco M, Mainardi F, Maggioni F, et al. Chronic paroxysmal hemicrania, hemicrania continua and SUNCT syndrome in association with other pathologies: A review. Cephalalgia. 2004;24:173-184.

- Removal of a pituitary adenoma - resolution of CH

Leone M, Curone M, Mea E, et al. Cluster-tic syndrome resolved by removal of pituitary adenoma: The first case. Cephalalgia. 2004;24:1088-1089.

Face/head/neck pains

- Pre-auricular pain – middle cranial fossa mass, infratemporal meningioma
- Trigeminal neuralgia – V1,2,3 distribution pain
- Glossopharyngeal neuralgia - Pain is typically experienced in the ear, base of tongue, pharynx, and tonsillar fossa and precipitated by coughing, chewing, or swallowing.
- Paraneoplastic syndrome related face/jaw pain - lung adenocarcinoma

  Ruffatti S, Zanchin G, Maggioni F. A case of intractable facial pain secondary to metastatic lung cancer. Neurol Sci. 2008;29:117-119.
- Severe facial pain ipsilateral to non-metastatic lung cancer - vagus nerve invasion

  Capobianco DJ. Facial pain as a symptom of nonmetastatic lung cancer. Headache. 1995;35:581-585.

Nummular Headache

- Continuous or intermittent head pain in an area of the scalp that is sharply contoured and fixed, round or elliptical, 1-6 cm in diameter
- One report of 60 yr F with left mastoid Nummular Headache, a left posterior meningioma; her headache resolved soon after subtotal resection of tumor.

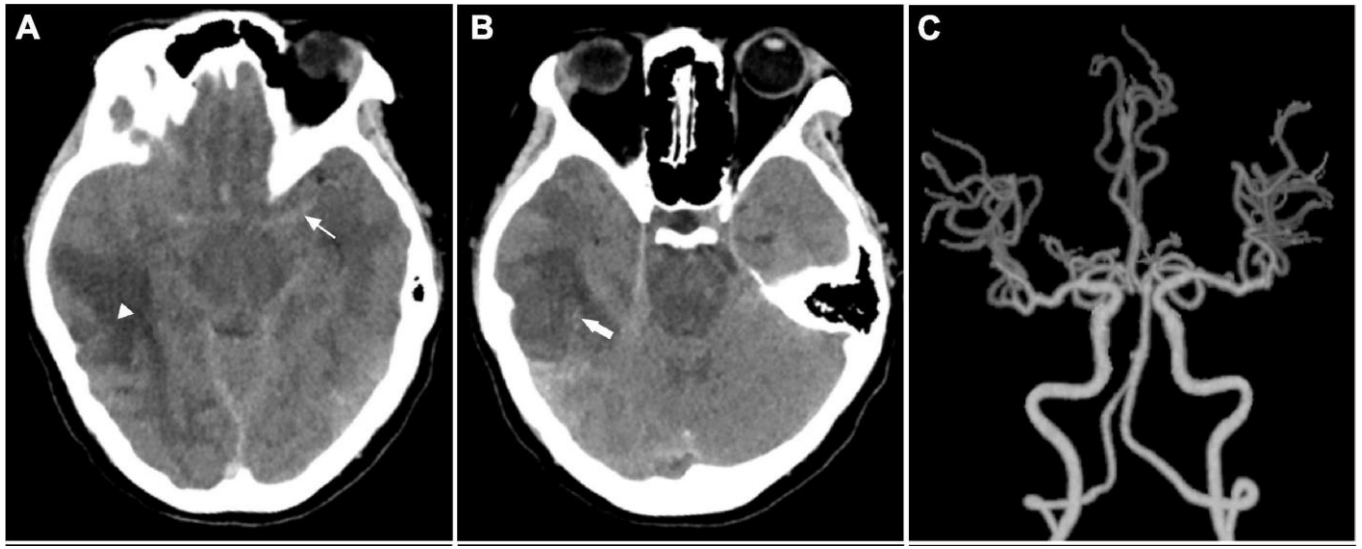
Guillem A, Barriga FJ, Gimenez-Roldan S. Nummular headache secondary to an intracranial mass lesion. Cephalalgia. 2007;27:943-944

Thunderclap headache

- Sudden onset - The pain of these severe headaches peaks within 60 seconds.
- Intracerebral hemorrhage or subarachnoid hemorrhage related to primary or metastatic brain tumor

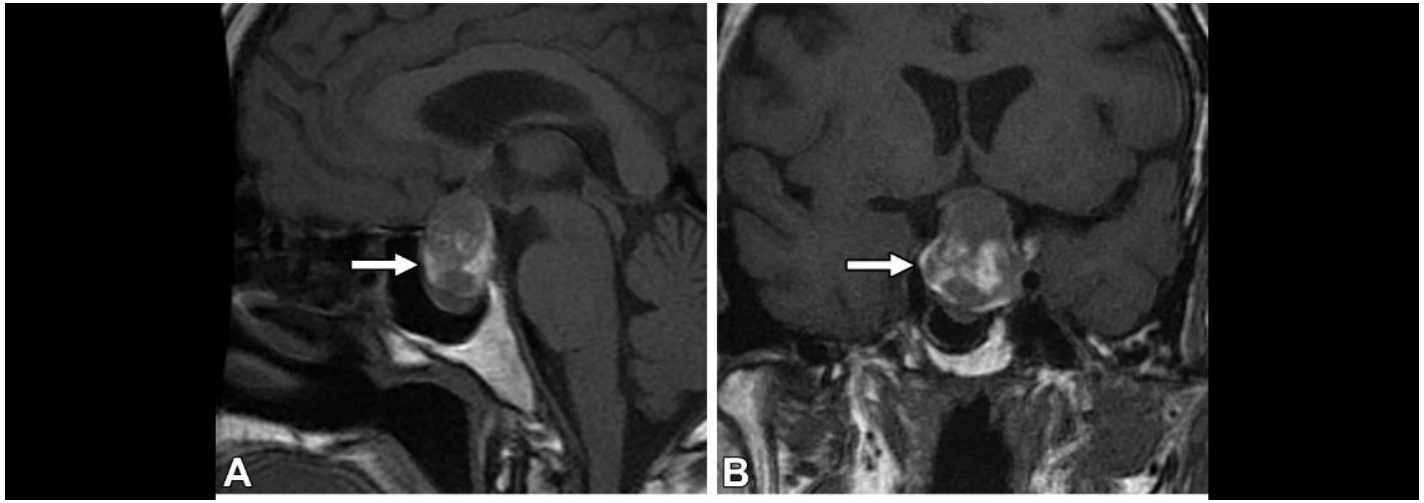
Navi BB, Reichman JS, Berlin D, et al. Intracerebral and subarachnoid hemorrhage in patients with cancer. Neurology. 2010;74:494-501.

Chen, Shijian, et al. "Cancer related subarachnoid hemorrhage: a multicenter retrospective study using propensity score matching analysis." Frontiers in Cellular Neuroscience 16 (2022): 19.

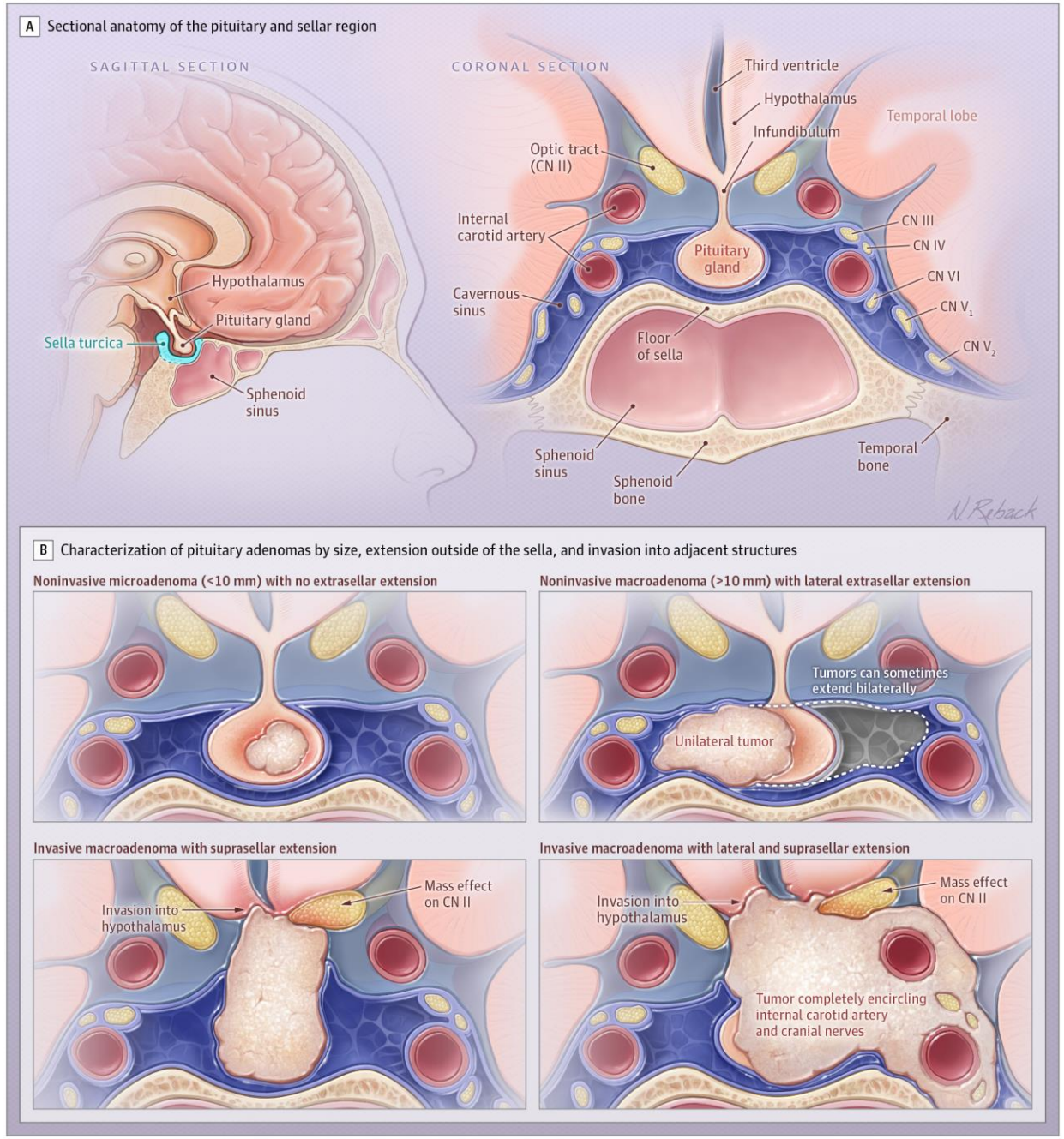


28-year- female with astrocytic glioma experienced SAH due to intratumoral hemorrhage in the first 11 days after the diagnosis of astrocytic glioma.
Tumor (white triangle), subarachnoid hemorrhage (thin white arrow) in **(A)**
intratumoral bleeding in **(B)**
normal cerebral arteries in **(C)**

Pituitary Adenoma



Primary Tumors of the Pituitary Gland: Radiologic-Pathologic Correlation
Robert Y. Shih, Jason W. Schroeder, and Kelly K. Koeller, RadioGraphics 2021 41:7, 2029-2046



JAMA. 2023;329(16):1386-1398. doi:10.1001/jama.2023.5444

Pituitary adenomas and Headache

- Pituitary adenomas are present in approximately 10% of persons in the general population on imaging studies or at autopsy. Approximately 99.9% of these are microadenomas

  Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med. 1994;120(10):817-820.

Direct cause of headache:

- Macroadenomas (>10 mm dia) - mass effect: visual field defects, headache, hypopituitarism
- 4% -10% pituitary apoplexy - hemorrhagic infarction of the tumor
  - Acute: severe headache of acute onset, visual field defects, and ophthalmoplegia
    - Predisposing factors include hypertension, pregnancy, major surgery, hypotension, dopamine agonist therapy, and anticoagulation therapy
      - Singh TD, Valizadeh N, Meyer FB, Atkinson JLD, Erickson D, Rabinstein AA. Management and outcomes of pituitary apoplexy. J Neurosurg 2015;122(6):1450–1457
  - Subclinical – chronic headaches
    - Zhang F, Chen J, Lu Y, et al. Manifestation, management and outcome of subclinical pituitary adenoma apoplexy. J Clin Neurosci. 2009;16:1273-1275.

Pituitary adenomas and Headache

Indirect cause of headache:

- Patients with somatotropinomas present with acromegaly.
- Arthropathy, consisting of early osteoarthritis (70% of patients) – cervicogenic HA
- Hypertension (35% of patients) – HTN HA
- Sleep apnea (65% of patients) – OSA HA

  Ben-Shlomo A, Melmed S. Acromegaly. Endocrinol Metab Clin North Am. 2008;37(1):101-122. doi:10.1016/j.ecl.2007.10.002

- Patients with thyrotropinomas present with symptoms and signs of hyperthyroidism – related HA

  De Herdt C, Philipse E, De Block C. Endocrine tumours: thyrotropin-secreting pituitary adenoma: a structured review of 535 adult cases. Eur J Endocrinol. 2021;185(2):R65-R74.

- Microprolactinomas - changes in estradiol levels
- During pregnancy, approximately 30.5% of patients with macroprolactinomas experience growth of the prolactinoma, with associated symptoms of vision loss and headache, compared with 15.2% of those with microprolactinomas.

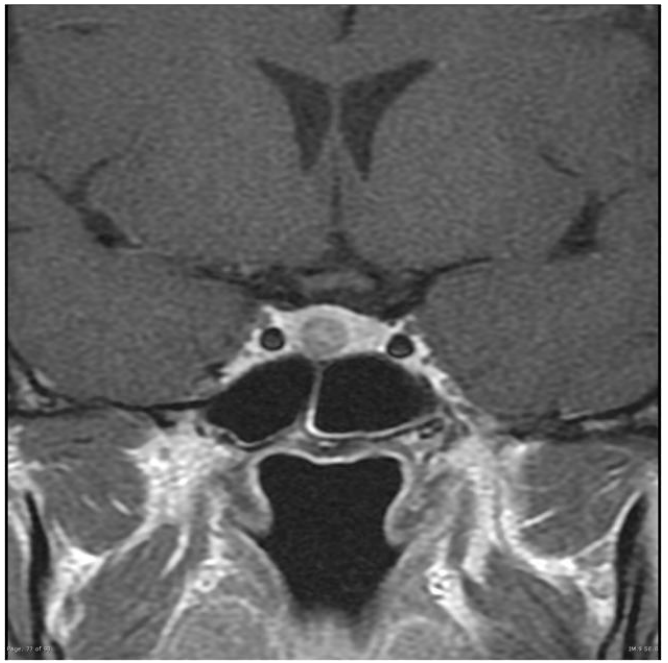
  Luger A, Broersen LHA, Biermasz NR, et al. ESE clinical practice guideline on functioning and nonfunctioning pituitary adenomas in pregnancy. Eur J Endocrinol. 2021;185(3):G1-G33.

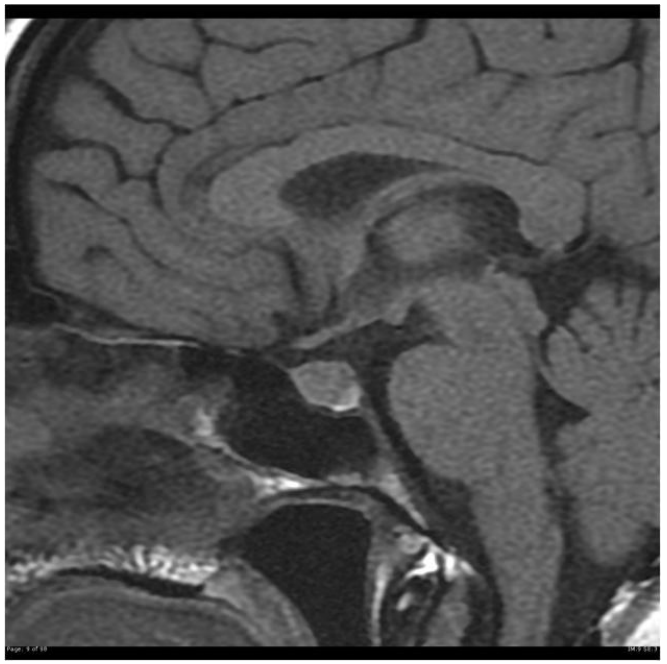
Diagnosis

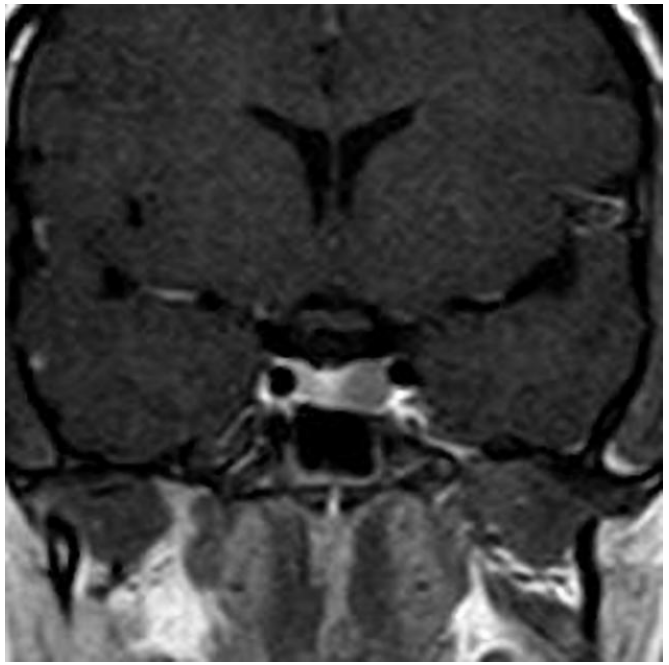
- CT can detect up to 80-90% of microadenomas between 5-10 mm in size

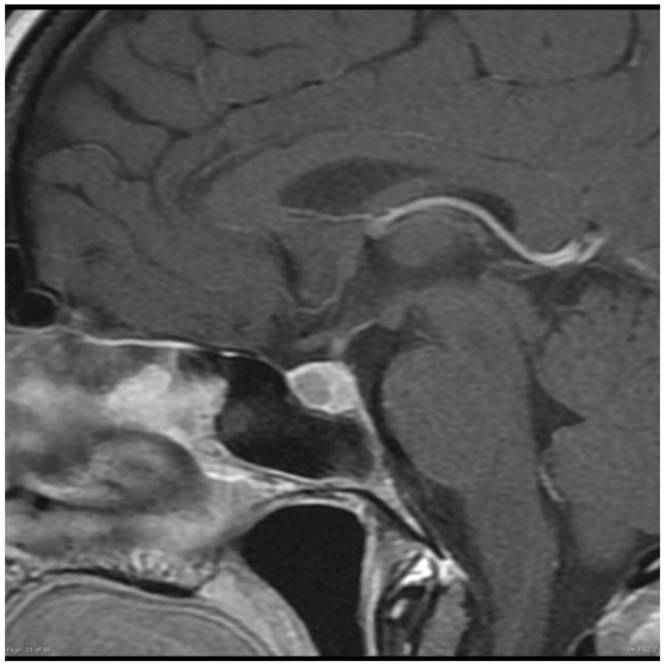
MRI

- **T1:** usually isointense to normal pituitary
- **T1 C+ (Gd)**
  - dynamic sequences demonstrate a rounded region of delayed enhancement compared to the rest of the gland
  - It takes 90 to 120 seconds for microadenoma to enhance while the normal anterior pituitary takes only 60 to 80 seconds to enhance
- **T2:** variable, but often a little hyperintense









Management

First-line therapy for pituitary adenomas is usually transsphenoidal surgery

Growth hormone-secreting adenomas

- Somatostatin analogues such as octreotide can dramatically improve headache, though interestingly can exacerbate headache in others

Colao A, Di Somma C, Pivonello R, et al. Medical therapy for clinically non-functioning pituitary adenomas. Endocr Relat Cancer. 2008;15:905-915.

Prolactinoma

- Bromocriptine (2.5-10 mg/d orally) and cabergoline (0.5-2.0 mg/wk orally) are approved by the FDA for treating hyperprolactinemia and prolactinomas
- Dopamine agonist therapy is first-line treatment for patients with prolactinomas, those with macroadenomas, or those who are considering pregnancy
- Dopamine agonists (cabergoline and bromocriptine) can worsen headache and cause nausea in some

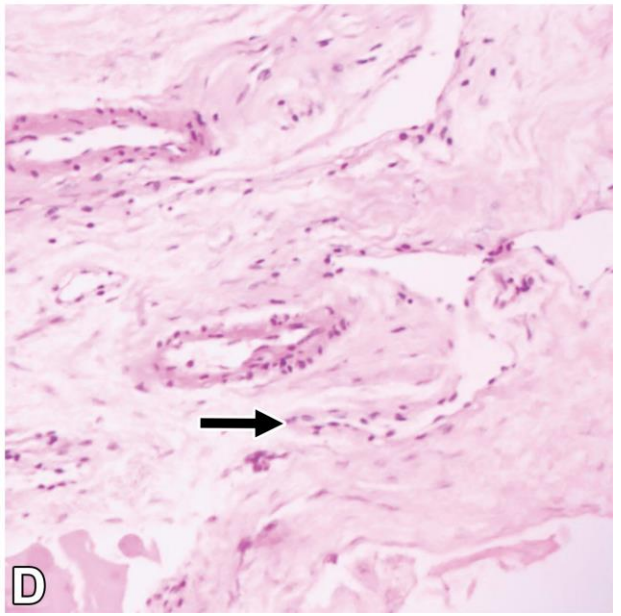
Yang MS, Hong JW, Lee SK, et al. Clinical management and outcome of 36 invasive prolactinomas treated with dopamine agonist. *J Neurooncol*. 2011;**104**:195-204.

Wang AT, Mullan RJ, Lane MA, et al. Treatment of hyperprolactinemia: a systematic review and meta-analysis. Syst Rev. 2012;1(1):33. doi:10.1186/2046-4053-1-33

Rathke Cleft Cyst

Rathke cleft cysts

- Rathke cleft cysts are benign fluid-filled growths that develop between the parts of the pituitary gland at the base of the brain
- They are congenital deformities
- Mass effect:
  - Vision changes
  - Frequent headaches
  - Nausea
  - Feelings of drowsiness or fatigue
  - Changes in personality or behavior, including confusion



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Craniopharyngioma

Craniopharyngioma

- Craniopharyngioma is uncommon, with an incidence of 0.13 per 100 000 person-years
- Adamantinomatous craniopharyngiomas (ACPs) account for 90% of craniopharyngiomas, while (squamous) papillary craniopharyngiomas (PCPs) represent the remaining 10%
- PCP is nearly always found in adults
- ACP has a bimodal distribution, peaking in children younger than 18 years of age and adults 40–60 years of age

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- Children: headache, vomiting, visual loss, lethargy, polydipsia and/or polyuria, and rarely cognitive and/or behavioral disturbances, endocrine dysfunction
- Adults: headache, vomiting, visual loss, lethargy, polydipsia and/or polyuria, cognitive and/or behavioral disturbances, endocrine dysfunction, weight gain

- Treatment of craniopharyngioma may consist of gross total or subtotal resection, plus or minus radiation therapy

Dandurand C, Sepehry AA, Asadi Lari MH, Akagami R, Gooderham P. Adult Craniopharyngioma: Case Series, Systematic Review, and Meta-Analysis. Neurosurgery 2018;83(4):631–641

https://radrounds.com/radiology-case-images-teaching-file/craniopharyngioma/

Headache Secondary to Brain Tumor Treatment

Medication/Radiation/Surgery

- Malignant gliomas – temozolomide (25% of pts get headache)
- Thalidomide, etoposide, imatinib, hydroxyurea, cisplatin, methotrexate, carboplatin, gemcitabine, capecitabine, carmustine, cediranib, and bevacizumab
- Intrathecal methotrexate and cytosine arabinoside - aseptic meningitis that can present with headache

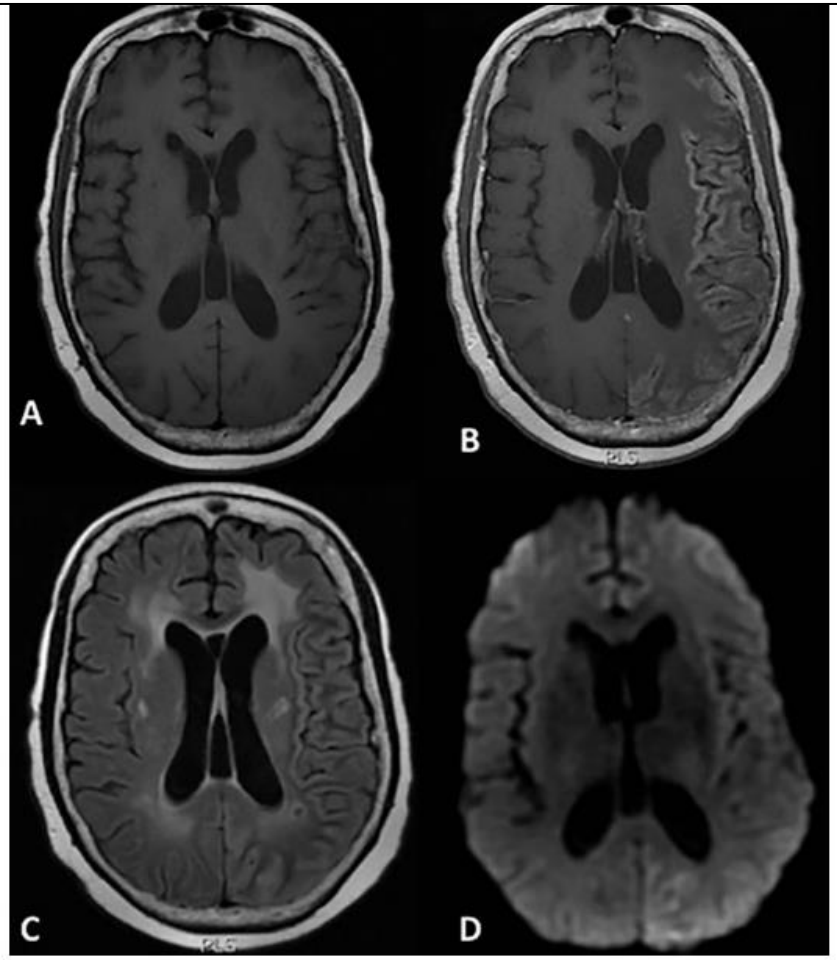
  Nelson, Sarah, and Lynne P. Taylor. "Headaches in brain tumor patients: primary or secondary?." Headache: The Journal of Head and Face Pain 54.4 (2014): 776-785.
- Post-craniotomy headache
- Occipital neuralgia related headache
- Radiosurgery
- Post surgery hydrocephalus

  Wan H, Chihiro O, Yuan S. MASEP gamma knife radiosurgery for secretory pituitary adenomas: Experience in 347 consecutive cases. J Exp Clin Cancer Res. 2009;28:36.

Stroke-like migraine attacks after radiation therapy (SMART) syndrome

- A 58-year-old female presented to the ED with a 2-day history of severe headache, right-sided hemiparesis, involuntary eye blinking, slurred speech, and confusion
- History of stage IV breast cancer with an isolated left frontal lobe brain metastasis.
- She had undergone surgical excision and brain irradiation therapy 8 years prior to presentation.
- CT and MRI - stable postoperative and radiation changes in the left frontal lobe
- The patient was admitted to the hospital, and initial CBC, blood culture, and paraneoplastic panel were negative.
- Initial lumbar puncture (LP) showed elevated white blood cells, and meningitis was suspected.
- CSF cultures showed no growth, and repeat LP on hospital day 6 was negative.
- The patient had continued episodes of confusion - concern for persistent seizures
- On hospital day 9, the patient had a witnessed seizure with eye blinking and right-sided facial twitching – treated with lorazepam

Repeat MRI exhibited new mild cortical expansion and enhancement, with increased signal on T2-weighted images and diffusion restriction involving the posterior left cerebral hemisphere



Magnetic resonance imaging on hospitalization day 9. Axial T1-weighted images through the level of the cerebral hemispheres before (A) and after (B) the administration of gadolinium contrast demonstrate diffuse gyral enhancement throughout much of the left cerebral hemisphere with some sparing of the frontal lobe, with corresponding mildly hyperintense signal on a T2/fluid attenuated inversion recovery image (C) and diffusion restriction on diffusion weighted imaging (D).

April D, Lall N, Steven A. Stroke-Like Migraine Attacks After Radiation Therapy Syndrome. *Ochsner J*. 2020;20(1):6-9.

Stroke-like migraine attacks after radiation therapy (SMART) syndrome

- SMART syndrome is a delayed complication of both whole brain irradiation and selective radiosurgery.
- The onset of symptoms varies from 1 to 37 years after initial radiation therapy, with an average 9.5 years

Black DF, Morris JM, Lindell EP, et al.. Stroke-like migraine attacks after radiation therapy (SMART) syndrome is not always completely reversible: a case series. AJNR Am J Neuroradiol. 2013. December;34(12):2298-2303.

Maloney PR, Rabinstein AA, Daniels DJ, Link MJ. Surgically induced SMART syndrome: case report and review of the literature. World Neurosurg. 2014. Jul-Aug;82(1-2):240, e7-e12.

- Typically associated with radiation doses of 50 Gy or more

Stroke-like migraine attacks after radiation therapy (SMART) syndrome

- Acute symptoms consist primarily of headaches, often with a migraine-like aura. Subsequently, patients often develop confusion, seizures, and stroke-like symptoms that may include motor deficits, paresthesia, aphasia, and visual disturbances
- Headache with photophobia and visual scintillations has been reported

  Pruitt A, Dalmau J, Detre J, Alavi A, Rosenfeld MR. Episodic neurologic dysfunction with migraine and reversible imaging findings after radiation. Neurology. 2006 Aug 22;67(4):676-8.
- Symptoms last from several hours to several weeks
- Typically reversible. A review of the literature, 83% of patients were reported to have had a complete recovery. Di Stefano et al reported full recovery in 85% (22/26) of patients, while 15% were left with permanent symptoms. Black et al reported that 45% (5/11) of patients in their case series had long-term symptoms, including cognitive impairment, hemiparesis, and dysphasia.

  Rigamonti A, Lauria G, Mantero V, Filizzolo M, Salmaggi A. SMART (stroke-like migraine attack after radiation therapy) syndrome: a case report with review of the literature. Neurol Sci. 2016. January;37(1):157-161.

  Di Stefano AL, Berzero G, Ducray F, et al.. Stroke-like events after brain radiotherapy: a large series with long-term follow-up. Eur J Neurol. 2019. April;26(4):639-650.

Treatment of the headache

- Manage underlying problem
- Corticosteroids
- NSAIDS, acetaminophen
- Neuropathic treatment options (ex: gabapentin)
- No data on migraine specific treatments – triptans, ditans, gepants, ergot, CGRP pathways medications

Other References

1. "Headache in Brain Tumors: A Systematic Review" by C. Amorim et al. published in Headache: The Journal of Head and Face Pain in 2016. This paper reviews the literature on headache as a symptom of brain tumors, including the frequency, characteristics, and potential mechanisms of tumor-related headaches.
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