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Abstract

Headache is one of the leading symptoms often associated with brain tumours. Secondary headaches attributed to intracranial neoplasias have been included in subchapter 7.4 of the third edition of the International Classification of Headache Disorders (ICHD-3). According to ICHD-3, the headache may be attributed to a brain tumour if it has developed in close temporal relation with the development of the neoplasia, has significantly worsened in parallel with the worsening of the tumour, and/or has significantly improved following the successful treatment of the neoplasia. Brain tumour headache was traditionally thought to display some specific clinical characteristics, including worsening in the morning and/or when lying down, being aggravated by Valsalva-like manoeuvres and accompanied by nausea and/or vomiting; however, the studies performed after the advent of modern neurodiagnostic techniques have pointed out that the "classic" brain tumour headache is uncommon, particularly at the time of clinical presentation. Therefore, it becomes critical to seek some specific factors associated with the presence of an intracranial mass (the so-called "red flags") that can guide the physician to establish an accurate diagnosis.

Keywords

International Classification of Headache Disorders, secondary headache disorders, tumour headache, magnetic resonance imaging study

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Introduction

Headache is probably the best-known symptom among those associated with brain tumours and patients with headache are often concerned that they may have an intracranial neoplasm. Nevertheless, headaches secondary to organic brain disease are uncommon, bearing a prevalence in the general population of 2.1% (1) and representing the 12.9% of patients evaluated at tertiary treatment sites (2); the vast majority of such cases consist of patients with medication overuse headache. Furthermore, headache is rarely the sole presenting symptom of a brain tumour. Instead, the headache is usually accompanied by other symptoms indicating a various involvement of the intracranial structures, such as personality changes, seizures, and/or focal neurological signs, along with signs of intracranial hypertension (nausea, vomiting, papilledema, blurred vision). Moreover, due to the development of accessible neuroimaging techniques, a diagnosis of intracranial neoplasm is reached earlier during the time course and the clinical picture of the associated headaches has significantly changed. The full-blown intracranial hypertension syndrome is by far less frequently seen than in the past. According to the studies performed after the advent of the modern neurodiagnostic techniques, the incidence of every type of headache in populations of patients affected by brain tumour ranges from 32% to 71% (3–8). There is a greater likelihood of headache being more common in children, in individuals with history of primary headache and in infratentorial and rapidly growing space-occupying lesions. Clinical characteristics of headache in brain tumour sufferers do not display pathognomonic features and most of the clinical diagnostic process relies on one or more associated "red" flags (9) (Table 1).

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Table 1. Red flags for brain tumour headache (9).

Headache with abnormal findings on neurological examination
New headache in a patient over 50 years
Headache with a history of cancer elsewhere
Pattern change or recent onset of headache
Progressive headache over days or weeks and atypical presentations
New-onset cluster headache or other trigeminal autonomic cephalgias
Headache brought on by exertion or Valsalva-like manoeuvre

Clinical characteristics of headache associated with brain tumours

The clinical characteristics of headache associated with brain tumours are fairly variable, according to several prospective clinical studies, depending on differences in the patient samples, study methodology, and intracranial tumour headache definition. The "classic" brain tumour headache has been described as a severe head pain occurring in the early morning, accompanied by nausea and/or vomiting, and improving in intensity over the course of the day. Other symptoms commonly described in association with the brain tumour headache are exacerbation by lying down or bending over and by Valsalva-like manoeuvres such as coughing, straining, and lifting heavy weights. Nevertheless, in an early prospective clinical study on adult brain tumour headache, the authors argued that this classic clinical syndrome is infrequently observed (4) and in a more recent clinical study the "classic criteria" were satisfied by only 5.1% of patients (5). More frequently, brain tumour headaches have non-specific or tension-headache-like features (10). Pain is usually localised bilaterally over the frontal regions (4–5), non-throbbing in quality (7–8) and moderate in intensity (5,7). Headaches are initially intermittent without a clear circadian distribution. Nocturnal headache exacerbation occurs in a small proportion of patients and is without a specific pathognomonic significance (4,11). According to a prospective study involving 206 adult patients (5), the majority of brain tumour headaches are considered "not classifiable", meaning that their phenotype did not satisfy the International Classification of Headache Disorders second edition (ICHD-II) diagnostic criteria for primary headache syndrome. On the other hand, 23.5% of patients could be classified as tension-type headache according the ICHD-II diagnostic criteria and 13.3% as migraine without aura. In all but one patient with a migraine-like brain tumour headache, there was at least one atypical clinical feature (middle-age onset, progressive pattern, association with Valsalva manoeuvre or exacerbation by lying down, nocturnal occurrence, unresponsiveness to analgesics).

The tumour localisation is not exactly predicted by the headache site but there is a trend toward a preferential frontal headache in supratentorial and skull base tumours, whereas occipital headache is more often seen in infratentorial ones. Patients affected by infratentorial tumours are more likely to develop nausea and vomiting, up to 42% in clinical series (4,5,7). It has been evidenced that patients with secreting pituitary adenomas or glioblastoma multiforme (GBM) are more often prone to develop a progressive headache as compared with those with other types of tumours (5), presumably due to a neuroendocrine mechanism in the first case and to a mass effect caused by the rapid growth of the neoplasm in the second.

It was commonly accepted that malignant gliomas were the tumours with the highest probability to be associated with headache (12), but recent studies have found that headache seems to be more common in metastatic brain tumours (6) or meningiomas (7) than high grade gliomas. Furthermore, a significantly high incidence of headache has been reported even in subjects with fast-growing pituitary adenomas (13).

Other risk factors associated with the development of headache besides the tumour types are localisation below the tentorium cerebelli (3,5,6,8,14) and a history of prior primary headaches (4,5,7). Among patients affected by primary headaches who eventually develop a brain tumour, more than half of them complained a relevant alteration of the pre-existing pattern (defined as change in frequency, localisation, severity or quality) (5,7). Furthermore, headache was reported in 64% of long-standing headache sufferers versus only 38% of individuals without a history of headache (5). A younger age at presentation is another risk factor for developing headache while having a brain tumour. According to Lowry et al. (15), the frequency of headache among patients affected by a malignant primary brain tumour was significantly higher in subjects younger than 45 compared with those 65 years or older (30% vs. 11%).

Although most patients exhibit non-specific headaches or, less frequently, a tension-type-like or a migraine-like headache, clinical pictures resembling that of less-common primary headaches has been described. Trigeminal autonomic cephalalgias (TACs), with a strictly unilateral, anterior headache often accompanied by cranial autonomic symptoms, including cluster headache, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and hemicrania continua, may complicate a space-occupying process, particularly if located in the pituitary or cavernous sinus regions (16,17). Almost all patients with secondary TACs

presented one or more atypical clinical feature at presentation or during the time course of the neoplasm.

On the other hand, cases of paroxysmal headache may occur with colloid cysts of the third ventricle or other pedunculated neoplasms that obstruct the flow of cerebrospinal fluid (CSF) at the level of the foramen of Monro. Headaches usually have a sudden onset, brief duration, variable localisation and are frequently precipitated by change in body position.

Remission of brain tumour-related headache occurs in most patients who undergo surgery, but it is not the rule. In a recent study on preoperative and postoperative headaches in patients affected by intracranial tumours (18), the prevalence of headache decreased from 52% at baseline to 43% and 30% at 1 and 6 months postoperatively, while worsening of the previous headache was observed in 19% and 9% at the 1 and 6-month follow up. No independent risk factor for worsening or new headache after surgery could be identified. On the contrary, younger age, female gender, low Karnofsky Performance Status (KPS), and tumor location in the occipital lobe were significant positive predictors for experiencing early postoperative relief (18).

On the other hand, craniotomy *per se* can cause postsurgical headache (19) that may persist in 32% of patients at a 6-month follow-up (20). Therefore, in the third edition of ICHD (21) headache remission is no longer considered an absolute criterion but only one of the three optional clinical characteristics forming criterion C of subchapter 7.4 (Table 2).

Diagnosis of headache associated to brain tumours

New or changed headaches are frequently observed in patients with brain tumours and are usually accompanied by other symptoms pointing toward an involvement of cerebral and meningeal structures; such as epileptic seizures, cognitive disturbances, focal neurological signs, and/or signs of intracranial hypertension. Furthermore, headache may be the presenting symptom in a percentage as high as about 50% of patients (6). Therefore, recognising a new or changed headache as the first manifestation of life-threatening process is crucial. According to ICHD-3 (21), headache can be attributed to intracranial neoplasm if it displays at least two of the following characteristics: i) headache has developed in close temporal relation to the tumour or led to its discovery; ii) headache has significantly worsened in parallel with worsening of the neoplasm and/or has significantly improved following the successful treatment of the neoplasm; iii) headache with at least one of four characteristics including progressive course, worsening in the morning and/or when lying down, aggravated by Valsalva-like manoeuvres, and/or accompanied by nausea and/or vomiting (Table 1). Since the headache in most individuals eventually found to be diagnosed with a brain tumour lacks specific characteristics, as outlined above, it is of maximal importance to make an early diagnosis; this can only be done by recognising some clinical clues, defined as "red flags", the presence of which raises the suspicion that

Table 2. Diagnostic criteria for headache attributed to intracranial neoplasm (ICHD-3 vs. our proposed new criteria).

ICHD-3 criteria	New proposed criteria
A. Any headache fulfilling criterion C	A. Any headache fulfilling criterion C
B. A space-occupying intracranial neoplasm has been demonstrated	B. A space-occupying intracranial neoplasm has been demonstrated
C. Evidence of causation demonstrated by at least two of the following:	C. Evidence of causation demonstrated by at least two of the following:
1. Headache has developed in temporal relation to development of the neoplasm, or led to its discovery	1. Headache has developed in temporal relation to development of the neoplasm, or led to its discovery
2. Either or both of the following:	2. Either or both of the following:
a) Headache has significantly worsened in parallel with worsening of the neoplasm	a) Headache has significantly worsened in parallel with worsening of the neoplasm
b) Headache has significantly improved in temporal relation to successful treatment of the neoplasm	b) Headache has significantly improved in temporal relation to successful treatment of the neoplasm
3. Headache has at least one of the following four characteristics:	3. Headache has at least one of the following four characteristics:
a) Progressive	a) Progressive
b) Worse in the morning and/or when lying down	b) worse in the morning and/or when lying down
c) Aggravated by Valsalva-like manoeuvres	c) Aggravated by Valsalva-like manoeuvres
d) Accompanied by nausea and/or vomiting	d) Accompanied by nausea and/or vomiting
D. Not better accounted for by another ICHD-3 diagnosis.	4. Any new kind of headache in oncologic patients with a cancer type prone to metastasis to the brain
	D. Not better accounted for by another ICHD-3 diagnosis.

the new or changed headache has a secondary origin that mandates urgent neuroimaging evaluation (9).

Pathophysiology

The most frequently cited cause of brain tumour headache is the presence of pressure or traction on intra- and extracranial pain-sensitive structures. It is common knowledge that brain parenchyma is insensitive to pain, because it lacks the presence of pain receptors, and that headache pain is triggered by surrounding structures. Indeed, possible mechanisms of headache attributed directly to neoplasm are traction on the veins with resulting displacement of venous sinuses, traction on the middle meningeal artery and on arteries at the base of the brain, direct pressure to cranial nerves with afferent pain fibers, or distension of intracranial and extracranial arteries (22). Traction acts either locally by the tumour mass impinging on pain-sensitive structures or distantly by extensive displacement of the brain (4). In both cases, traction results from the expansion of tumour tissue or the presence of edema and/or secondary hemorrhage. According to Loghin and Levin (23), the growth-rate of space-occupying lesions plays an important role in predicting the occurrence of traction and headache pain. Headache would be more frequent and early in onset in fast-growing tumours, because the intracranial space does not have a chance to adapt to the increased pressure (10). Another important feature that predicts whether headache will occur is tumour location. Tumours that typically provoke headaches include intraventricular, midline, and posterior fossa lesions. They can all produce an obstruction of cerebrospinal fluid drainage causing hydrocephalus and dislocation of the periventricular nociceptive structures (18,24); however, many pathophysiological aspects remain unclear. Even in tumours of apparently the same size, location, and histological type, the accompanying headache may be very different and sometimes may not be present at all (6). Furthermore, in certain situations, little or no direct mass effect on pain-sensitive structures from tumours might still result in headaches (24). In addition to the classic "traction hypothesis", in recent years other mechanisms have been suggested, including central sensitisation of second-order trigeminovascular neurons, chemical pronociceptive effects of tumours affecting the nociceptive afferents, and, at least in patients with secreting pituitary adenomas, direct effect of hormone production. The central sensitisation of second-order trigeminovascular neurons is the result of prolonged irritation from pericranial structures and can lead to development of refractory headache pain. Considering that nociceptive activity entering spinal and trigeminocervical neurons are subject to modulation by descending inhibitory efferents arising from brainstem nuclei (including the periaqueductal gray, the locus coeruleus and the nucleus raphe magnus), dysfunctional descending pain-modulating circuits are also believed to play an important role in the maintenance of prolonged headache pain. The possibility that central sensitisation and/or deficient brainstem inhibition may contribute to the pathogenesis of brain tumour headache is still being debated; but it would offer an explanation for why surgical debulking does not always lead to remission of neoplastic headache pain (10).

It has been posited that the tumour itself may produce substances critical for the development of head pain. These may include nitric oxide synthase, calcitonin gene-related peptide, tumour necrosis factor alpha, vasoactive intestinal peptide and many others (25). The pro-inflammatory agents released by brain tumours are in addition to the chemical soup already present as a result of prolonged mechanical irritation of pain-sensitive structures (10). In a recent study (26), an increase of substance P and of prostaglandin E2 concentration within meningiomas was associated with higher preoperative pain intensity.

Treatment of headache associated to brain tumours

Since brain tumour headache usually disappears or improves after surgery (5,6), although in a minority of patients it may persist or even get worse (18), its therapy is mainly based on treatment of the underlying tumour, unless contraindicated for a presumed high risk of morbidity and mortality, particularly in the case of benign tumours. In cases of patients who are medically unfit for surgery or in whom the risks of surgery outweigh the benefits, a conservative approach should include prevention and management of medication overuse. Since patients with a history of a primary headache disorder more frequently exhibit brain tumour-related headaches, conventional therapy of the original headache should be employed (27). Although studies describing clinical efficacy of preventive therapies in patients with migraine-like headache and intracranial neoplasms are not available, single reports showed possible efficacy of triptans in one case of glioblastoma (28) and in two cases of pituitary macroadenoma (29,30).

Before the operation or when surgery is not indicated, the therapy of headache usually aims to control intracranial hypertension secondary to brain oedema.

Brain swelling from the tumour is traditionally treated with corticosteroids. Among corticosteroids dexamethasone displays the highest potency, being

nearly six times as potent as prednisone, and is considered the drug of choice due to a half-life of 36–72 hours, limited mineral corticoid effect and reduced inhibition of leucocyte migration (23,31).

Dexamethasone is administered at the usual dose of 2–4 mg twice daily, although an initial dose of 10 mg intravenously followed by 4 mg every 6 h may be used for limited periods (32,33). However, the clinical efficacy of corticosteroids in relieving headache in tumours not complicated by brain oedema or mass effect is still controversial. Other anti-oedema therapies include osmotic and diuretic agents such as mannitol and furosemide that are usually administered in association with corticosteroids, although without firm evidence of efficacy. In the case of documented hydrocephalus, procedures of ventricular drainage and/or ventricular shunting are indicated, although a higher rate of complications has been observed as compared with individuals affected by non-neoplastic pathologies (34). If no oedema is present or in patients who do not achieve significant pain relief from corticosteroid therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) and/or opioids may be added. Since patients with secondary headache with a migraine or tension-type headache phenotype are equally prone to medication overuse headache, particular attention should be paid in prevention and management of this complication, although its real incidence in brain tumour cohorts is not currently known. Relapse of the headache after a period relatively free of pain may herald recurrence of the tumour, although the exact predictive value of recurrent headaches is not known. Patients with metastatic disease are usually treated with whole brain radiation in addition to corticosteroids, while in the case of a single or a limited number of metastases (no more than three), stereotactic radiosurgery or surgical resection may be a choice, the former being preferable in patients with metastases less than 3–3.5 cm in diameter (35). In a recent study on patients with brain metastases, palliative radiotherapy relieved headache in 41% of cases (36). Conventional chemotherapy may be the initial treatment for patients with brain metastases from chemosensitive tumours such as small cell lung carcinoma (SCLC) or breast cancer, while innovative targeted immunotherapies are now available for a number of neoplasms including melanoma (37) and renal cell carcinoma (38).

Discussion

Classification of secondary headaches must be specific enough to avoid overdiagnosis of incidentalomas that would expose patients to the risk of inappropriate and even dangerous interventions. On the other hand, diagnostic criteria should also be sensitive enough to prevent secondary headaches from being misdiagnosed as primary ones, thus precluding the possibility of a curative treatment. However, it is important to emphasise that surgical treatment for brain tumours is rarely performed solely for pain relief, even when a clear evidence of causation exists.

The problem with the diagnostic criteria for brain tumour headache (as for all secondary headaches) is criterion C, which establishes a clear causality relationship. For most secondary headaches the causality depends on the temporal association between the headache and the pathologic process. Previously, in ICHD-2 (39), criterion D required that the headache should improve or disappear after treatment of the secondary cause. In ICHD-3 (21), this item is no longer essential, having been "downgraded" to a sub-criterion under C. As Olesen et al. (40) pointed out, one of the main purposes of diagnostic criteria is to enable a diagnosis at the onset of a disease in order to guide treatment. In this context, a classification that allows definitive diagnosis of a secondary headache only after it has abated may serve the purpose of science but not of clinical medicine (40).

Furthermore, with regard to brain tumours, it is possible that some of the patients who still complain of headache after surgery actually suffer from post-craniotomy headache (5), leading to an inaccurate understanding of the etiology of their pain. On the contrary, some patients with primary headache undergoing surgery for an incidental finding may experience sustained improvement of their headache due to a placebo effect (5). Therefore, we could argue that by "downgrading" former criterion D in the classification of brain tumour headache, ICHD-3 has gained in sensitivity without significant decrease in specificity.

As for nearly all secondary headaches, the ICHD-3 diagnostic criterion A for *headache attributed to intracranial neoplasm* includes headache of any type, thus being less restrictive than the corresponding one in ICHD-II, which required the presence of specific headache characteristics (41). Ultimately, ICHD-II criterion A underwent the same fate as criterion D, having now been "downgraded" to a sub-criterion under C, which mentions "specific" brain tumour headache characteristics. The major problem here is that true specificity is difficult to assess, as most studies on the occurrence and characteristics of brain tumour headache are based on cohorts of patients with a known brain tumour. Furthermore, many of these studies have pointed out that brain tumour headaches lack distinct features and that they may also mimic a variety of primary headache types (4,5,8).

To improve sensitivity of criterion C, we suggest adding a fourth sub-criterion (Table 2), which provides the possibility of any new kind of headache in

populations with *a priori* increased risk of brain tumours, such as oncologic patients with a cancer type prone to metastasis to the brain (42,43).

The reasoning behind this proposal may be clarified thinking about two similar clinical scenarios. Although the decision to investigate headache is based on a number of complex factors, a common approach to a young adult with recent onset of isolated headache with a tension-type phenotype is to manage the symptom and to monitor the evolution (44). If this patient harbours a malignant tumour (for example a high grade glioma), in the following weeks headache may significantly worsen, prompting neuroimaging execution: In this context, a definitive diagnosis of headache attributed to intracranial neoplasm could be made even in the absence of "typical" clinical characteristics (sub-criterion 3 of criterion C), having still satisfied two out of three sub-criteria of criterion C; that is, headache leading to neoplasm's discovery and headache worsening in parallel with worsening of the neoplasm (21). In the exact same situation, if patient would have a history of breast cancer, almost every clinician would decide to investigate headache at once, thus discovering the neoplasm (a metastasis, in this case) before headache could get worse; in this context, a definitive diagnosis of headache attributed to intracranial neoplasm could not be made in the absence of "typical" clinical characteristics (21). Adding the aforementioned fourth sub-criterion would compensate for the loss of ICHD-3 diagnostic criteria sensitivity that may occur in such situations.

Key findings

- In most patients, brain tumour headaches lack distinct features.
- In headache sufferers, the suspicion of underlying brain tumour relies on the presence of certain "red flags".
- The addition of a new sub-criterion; that is, oncologic history, may improve sensitivity of classification.

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