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Brain Tumour Related Headache: Features, Pathophysiology and Management Strategies

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Abstract

Introduction. Brain tumours constitute approximately 1% of all newly diagnosed cancers. Their manifestation typically involves headache, neurological impairment, focal onset seizures and syndromes related to tumour location. Severe headache presents as a prevailing symptom and occurs in over 50% of patients. Brain tumour associated headache exerts significant effect on quality of life in cancer patients. The following article aims to provide a comprehensive overview of most common and promising brain tumour related headache treatment strategies.
State of knowledge. Headache in brain tumour patients arises from traction or displacement of intracranial pain-sensitive structures, such as vascular tissue, dura mater or periosteum. This can be caused by tumour's mass itself, by tumour associated oedema or as a sequela of anti-tumour treatment. Most common therapeutic modalities include tumour surgical resection, cerebral oedema management, radiotherapeutic interventions and

administration of analgesic agents. Complete removal of the tumour stands as the most effective approach, often bringing substantial alleviation in majority of cases.
Conclusion. Headache affects the majority of individuals afflicted by brain tumours. Not all patients are suitable candidates for the resection of the underlying neoplasm. In such instances, the application of alternative approaches might be beneficial. Ongoing and future investigations may enhance the development of novel treatment strategies, possibly influencing the well-being of cancer patients, especially within palliative care area.

Keywords: Brain tumour, Headache, Therapy, Surgery, Radiotherapy, Pharmacotherapy.

Introduction

Brain tumours represent approximately 1% of all newly diagnosed cancers [1, 2]. According to the 2016 *World Health Organization Classification of Tumours of the Central Nervous System*, there are over 100 histologic subtypes of brain tumours [3]. These include astrocytic tumours, ependymal tumours, oligodendroglial tumours, choroid plexus tumours, meningiomas and embryonal tumours. Gliomas represent the most prevalent primary brain tumours, accounting for over 50% of cases [1]. The incidence of primary malignant brain tumours is considerably variable across different regions of the world. The highest incidence rates are observed in Northern Europe, followed by the United States, Canada, and Australia. Conversely, Southeast Asia, East Asia, and India exhibit the lowest incidence rates of these tumours [4].

Brain tumours are usually symptomatic and present with a severe headache, progressive neurological deficits, most commonly motor weakness, focal onset seizure and additional deficits in brain function related to the location of the tumours, such as frontal lobe associated abulia and dementia or occipital lobe associated visual field defects. The prevalence of headache in brain tumour ranges between 32 and 71% [5]. Both primary and secondary tumours are equally likely to cause headache [6]. The typical presentation of brain tumour headache is characterized by progressive severe pain, worse in the morning accompanied by nausea and vomiting. Although these features may resemble tension-type headache, tumour related headache is often exacerbated by coughing, straining or bending forward, as opposed to tension-type headache [6]. Additional presence of neurologic deficits or focal seizures is a key factor to differentiate brain tumour headache from others.

Brain tumour related headache may significantly affect the quality of life in cancer patients. The management depends on several factors, including the type of tumour, the patient's functional status or the stage of the disease [7]. Most common treatment options for brain tumour headache include surgical intervention, radiotherapy, chemotherapy, anti-oedema therapy or analgesic agents. This article aims to provide a comprehensive overview of the most frequently employed approaches for a relief in headache related to brain tumours.

Materials and Methods

Data for the present study was acquired through a review of existing literature and identification of relevant publications. This was performed by conducting a search of PubMed database using "(Brain Tumour OR Brain Neoplasm OR Intracranial Neoplasm) AND Headache AND (Therapy OR Management OR Treatment)" as a search query.

Brain Tumour Headache Mechanism

The brain parenchyma itself does not have pain receptors and is therefore insensitive to pain. Instead, pain receptors within the skull are mainly located in the surrounding vascular tissue, dura mater, periosteum, and intracranial segments of cranial nerves [8]. Pain is typically a response to traction or displacement of these structures caused by intracranial hypertension resulting from oedema around the tumour, tumour growth or tumour apoplexy [9]. In certain tumours, particularly those in sellar region, significant mass effect may not be present and headaches might be attributed to direct proximity to the cavernous sinus or the pain-inducing effects of somatostatin or dopamine produced by the tumour [10, 11]. The characteristics of headache are related to the growth rate of the tumour, with sharp and intense pain typically occurring in fast-growing tumours, while mild and intermittent pain is more common in slow-growing ones [12, 13].

In addition, worsening or newly acquired headache can be a consequence of the anti-tumour management itself, sometimes observed after craniotomy, radiotherapy or pharmacological treatment. Radiotherapy induced headache can manifest acutely or with a delay, usually occurring within a period of 2 weeks to several months after radiation [7]. Common chemotherapeutic medications used in systemic brain tumour treatment are also a frequent cause of treatment-associated headache. Temozolomide, used in malignant gliomas and brain metastases is reported to cause headache in up to 25% of patients [14, 15]. Furthermore, agents used in palliative care, such as ondansetron, which prevents chemotherapy induced nausea and vomiting, has been reported to cause headache in 14 to 39% of patients [16].

Table 1. Headache red flags warranting the need for further investigation.

New, severe headache or headache that changed over time
Headache awakening the patient from sleep or occuring in the morning after waking
Headache associated with nausea and/or vomiting without migraine
Headache accompanied by focal neurologic symptoms or seizures
Progressive in nature headache
Blurred vision, papilledema, diplopia
Headache not resembling any of the primary headaches
New acute headache onset in elderly or in children
Headache with meningismus
Headache exacerbated by bending forward, coughing, sneezing or straining

Management Strategies

Anti-oedema treatment

Brain oedema is a prominent characteristic of brain tumours and significantly contributes to patient's clinical state through whole disease period. Headache is a common

symptom in patients with brain oedema and arises from traction or pressure on intracranial pain-sensitive structures [9]. In a large patient series with brain tumour related oedema, up to 60%

of patients reported experiencing headaches. The intensity of pain is often associated with the size and location of the tumour, the amount of oedema surrounding the tumour and presence of midline shift [6, 13]. Brain tumour related oedema is primarily extracellular and results from increased capillary permeability and pressure gradient, which lead to plasma leak into the brain parenchyma [17].

Table 2. Headache attributed to intracranial neoplasia according to The International Classification of Headache Disorders 3rd edition.

A. Any headache fulfilling criterion C
B. Intracranial neoplasia has been diagnosed
C. Evidence of causation demonstrated by one or more of the following:
1. headache has developed in temporal relation to the intracranial neoplasia, or led to its discovery
2. headache has significantly worsened in parallel with worsening of the intracranial neoplasia
3. headache has significantly improved in temporal relation to successful treatment of the intracranial neoplasia
D. Not better accounted for any other ICHD-3 diagnosis.

Treatment of brain tumour oedema allows to achieve remarkable pain relief as well as possible withdrawal of neurologic deficits, and is typically started before definite tumour management is initiated [18]. The preferred, classical approach is corticosteroid therapy, with dexamethasone being the steroid of choice. Dexamethasone is routinely administered in dosage of 4 mg/day or 16 mg/day in 4 equal doses [19]. Dexamethasone has shown to be approximately six times as potent as prednisone and reaches full effect within 24 to 72 hours [17].

Although the exact mechanism of action is not known, various mechanisms have been proposed, including phospholipase A2 inhibition, improvement of peritumoral microcirculation and reduced expression of oedema producing vascular endothelial growth factor (VEGF) [20].

In cases of severe oedema, osmotherapy with mannitol or glycerol may also be employed. A standard dose of 20% mannitol solution (1g/kg) effectively reduces intracranial pressure by 30 to 60% for 2-4 hour [17]. However, studies show that osmotherapy usefulness in tumour related brain oedema is uncertain. Rapid osmotherapy accompanied by tumour

compromised brain-blood barrier may greatly increase the risk of osmotic agent escape into brain parenchyma and in result gradient reverse followed by water re-entry into the brain [17].

Recent investigations have explored novel therapeutic approaches for brain tumour oedema. These include the use of corticotropin releasing factor, selective VEGF inhibitors, and selective cyclooxygenase-2 inhibitors. In animal studies, these agents have shown promising outcomes in controlling oedema without significant adverse effects when compared to dexamethasone [21-23]. Further studies are necessary to establish safety and efficacy of these interventions.

Surgical Intervention

Surgery is considered the most effective approach for definitive treatment of brain tumour, and complete resection should always be the goal, and as described in the *International Classification of Headache Disorders* (ICHD), headache attributable to brain tumour resolves after successful neoplasm treatment [24]. In a study conducted by Pfund et al. [13] out of 164 brain tumour patients who reported preoperative headaches, 139 (84,8%) of them reported an improvement in their symptoms, of which 126 (76,8%) became completely pain free. Similarly, Valentis et al. [25] observed that out of 111 patients with preoperative headaches, surgery brought improvement in 98 (88,3%) cases, while the remaining 13 patients had persistent headache that was probably not attributed to the brain tumour. In a prospective cohort study conducted by Munkvold et al. [26] 507 brain tumour patients who underwent surgery were monitored for up to 6 months postoperatively with focus on headache change. At the 6-month follow-up, 250/357 (70%) patients reported the absence of any pain, while 40/357 (11,2%) reported moderate to severe headache. The authors identified a statistically significant association between early postoperative headache improvement and the location of the tumour in the occipital lobe, tumour volume, younger age, gender and preoperative Karnofsky Performance Status.

Persistent postoperative headache is most often attributed to the craniotomy-related pain [27]. The highest incidence of craniotomy associated headache has been documented in suboccipital craniotomies and retrosigmoid approach, especially in the management of vestibular schannomas [28-30]. The pain is typically described as mild to moderate and does not significantly affect daily activities, and resolves gradually over time. However, in some cases, treatment is required, usually in form of anti-inflammatory agents, sometimes followed by narcotic drugs such as morphine, codeine or hydrocodone [27, 31].

In cases of patients who are medically unfit for surgery or in whom the risks of surgery outweigh the benefits , surgical intervention in form of ventriculoperitoneal shunting may be considered as a palliative treatment option for the relief of increased intracranial pressure associated symptoms, including headaches. Nigim et al. [32] conducted a study involving 59 patients with hydrocephalus in the setting of brain metastasis or primary tumour who underwent ventriculoperitoneal shunt placement. At the most recent follow-up, out of 36 patients who reported headache, 32 reported significant improvement. Ventriculoperitoneal shunting has been found to be helpful in achieving rapid and long-lasting stabilization of intracranial pressure in cases of serious clinical deterioration and failure to achieve improvement with pharmacological treatment and could be considered as a supplementary method in palliative pain management.

Radiotherapy

When definitive treatment is contraindicated due to multiple brain metastases or other factors, radiotherapy is considered a viable option in palliative care, particularly for pain alleviation.

Whole brain radiotherapy (WBRT) is a commonly used approach for patients with surgically inaccessible multiple metastases. It can be administered as a preventative, therapeutic or palliative agent, and has shown to be effective in pain relief in the majority of cases [33]. Various studies have demonstrated that palliative WBRT can result in an improvement of headache associated discomfort in 82% of patients on average [34, 35]. However, symptoms relief may not be permanent, as approximately 26% of patients with initial response reports symptoms recurrence [35]. Furthermore WBRT is also associated with serious adverse effects that greatly impair patient's quality of life. Even with appropriate fractionation of therapy, WBRT may lead to worsening of headaches in the early stages and significant cognitive dysfunction in the late phase [36].

In selected patients, minimally invasive radiotherapy in form of stereotactic radiosurgery can be a viable option for achieving control of brain metastases. Unlike whole brain radiotherapy, radiosurgery has less risk of causing acute toxicity or long-term cognitive impairment [37]. It can be used as a standalone palliative treatment or in combination with whole brain radiotherapy or surgical resection to improve survival rates. While there is limited data regarding the efficacy of radiosurgery in headache relief, it has been shown to significantly improve patient quality of life and reduce the doses of WBRT, thereby potentially avoiding associated adverse effects [38].

Pharmacological Analgetic Agents

In cases of adjuvant therapy induced pain, absence of brain oedema or failure of corticosteroid therapy to provide pain relief, simple analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) might be adequate for headache control. In some cases of severe chronic headache, opioid narcotics may also be necessary for optimal analgesic effect. Opioid management in brain cancer patients is complex, especially in those with multiple brain metastases who commonly suffer from renal or hepatic failure [39]. Opioid administration in the setting of renal or hepatic failure can lead to serious adverse effects such as respiratory or central nervous system toxicity due to active metabolite accumulation [40]. For instance, special caution must be taken with morphine use in renal failure [41] as well as methadone or tramadol in liver failure [42]. In the setting of concurrent liver and renal failure fentanyl and hydromorphone appear to be the best choices [40]. Significant concern in outpatient opioid prescription is the potential for addiction and drug abuse. A recommend approach in chronic pain therapy is to combine a long-acting opioid with a short-acting agent for breakthrough pain. Long-acting opioid such as transdermal fentanyl system, sustained-release morphine or buprenorphine have a lower potential for abuse and are reasonable choices for long-term pain management [43]. Safe and effective use of opioids can be unsured by careful clinical assessment and frequent patient follow-up.

In severe unresponsive headaches, which are often not directly attributable to brain tumour itself, but rather to adjuvant chemotherapy, additional or alternative management approaches may be required. Cannabinoids, that are sometimes used as co-analgesics in cancer patients might be of use [44, 45]. Brain tumours cells have been shown to express higher levels of CB1 and CB2 cannabinoid receptors [46-48], making them possibly more susceptible to the effects of cannabinoids and several animal studies have documented the activation of various pathways in brain tumour cells that can lead to pain alleviation [49]. A recent review [50] found that compared to placebo, cannabinoid administration was associated with a greater average number of patients who experienced not only pain reduction, but also relief from nausea and vomiting. While further research is needed to establish the use of cannabinoids in brain tumour patients, evidence suggests that cannabinoids have a safer profile than opioids and may be a viable option for pain management.

Conclusion

Headache is one of the most prevalent symptom of a brain tumour and is often accompanied by other signs, such as focal neurologic deficits, seizures and nausea or

vomiting. It is believed to arise from the irritation of intracranial pain-sensitive structures or to be a consequence of tumour treatment. Brain tumour associated headache can have a significant negative influence on patient's quality of life and the most effective treatment method is management of the underlying tumour, preferably through surgery. Pain alleviation may also be achieved through adjuvant therapy, such as radiotherapy, anti-oedema treatment or administration of analgesic medications. Many aspects concerning pain-relieving mechanisms as well as causes of pain recurrence in brain tumours are still not fully understood. Future and ongoing research may however provide insight into these factors and lead to the development of new management approaches, particularly useful in the context of cancer palliative care.

Authors contribution.

Conceptualization - Patrycja Doruch, Michał Senger; Methodology - Patrycja Doruch, Michał Senger; Formal Analysis – Patrycja Doruch, Michał Senger, Karolina Rogacka; Investigation – Patrycja Doruch, Michał Senger, Karolina Rogacka; Resources – Patrycja Doruch, Michał Senger, Karolina Rogacka; Data Curation – Michał Senger; Writing - rough preparation – Patrycja Doruch, Michał Senger, Karolina Rogacka; Writing - review and editing – Patrycja Doruch, Michał Senger, Kornelia Kędziora-Kornatowska, visualization – Patrycja Doruch, Michał Senger ; Supervision – Kornelia Kędziora-Kornatowska.

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