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ORIGINAL ARTICLE

What are the headache features associated with brain metastases in patients with systemic cancer?

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Abstract

Objective: *The objective of the study was to identify if headache characteristics and accompanying signs or symptoms are associated with brain metastases (BM) in patients with non-central nervous system (CNS) cancer.* **Materials and Methods:** *Patients with systemic cancer and headache seen at a single center between June 2012 and June 2018 were included in the study. Hematologic or primary CNS tumors were excluded from the study. Simple and multiple logistic regression analyses were used to measure associations with BM.* **Results***: From 572 patients with cancer and headache, 216 (38%) were diagnosed with BM. Characteristics associated with BM were male sex [odds ratio (OR) = 1.9], headache starting after cancer diagnosis (OR = 2.1), oppressive type (OR = 1.9), presence of vomiting (OR = 5.8), not increased by changes in position (OR = 2.2), and generalized location (OR = 0.34). In addition, having another symptom/sign other than headache was seen in 73% of patients with BM and was significantly associated with higher odds of BM (OR = 6.08), especially if patients presented with altered mental status (OR = 15), visual complaint (OR = 15), focal motor weakness (OR = 11), seizures (OR = 15), ataxia (OR = 19), or vertigo (OR = 3.8).* **Conclusion***: To assess their odds of being diagnosed with BM, the attending team should consider the characteristics of the headache and any accompanying symptoms and signs.*

Keywords: *Headache. Brain metastases. Systemic cancer.*

¿Cuáles son las características clínicas asociadas de las cefaleas con metástasis cerebrales en pacientes con cáncer sistémico?

Resumen

Objetivo: *Identificar si las características de la cefalea y sus síntomas y signos acompañantes se asocian a metástasis cerebrales en pacientes con cáncer sistémico.* **Material y Métodos***: Pacientes con cáncer sistémico y cefalea vistos en un centro nacional de referencia entre junio 2012 y junio 2018 fueron incluidos. Se excluyeron pacientes con tumores primarios del SNC y con neoplasias hematológicas. Se realizaron regresiones logísticas simples y múltiples para medir la asociación entre las características clínicas y la presencia de metástasis cerebrales.* **Resultados:** *Se incluyeron 572 pacientes con cáncer*

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y cefalea, de los cuales, 216 (38%) fueron diagnosticados con metástasis cerebrales. Las características asociadas con metástasis cerebrales fueron género masculino [Razón de momios (RM) = 1.9], cefalea que inició después del diagnóstico de cáncer (RM = 2.1), tipo opresivo (RM = 1.9), presencia de vómito (RM = 5.8), que la cefalea no incrementara con cambios en la posición (RM = 2.2), y localización generalizada (RM = 0.34). Adicionalmente, el presentar otro síntoma o signo además de la cefalea se documentó en el 73% de los pacientes con metástasis cerebrales y fue significativamente asociado con una mayor probabilidad de metástasis cerebrales (RM = 6.08); especialmente cuando presentaron alteración del estado de alerta (RM = 15), queja visual (RM = 15), déficit motor (RM = 11), convulsiones (RM = 15), ataxia (RM = 15), o vértigo (RM = 3.8). **Conclusión:** *Al evaluar la posibilidad de tener el diagnóstico de metástasis cerebrales, el equipo encargado de la atención de los pacientes deberá considerar las características de la cefalea y los síntomas o signos acompañantes.*

Palabras clave: *Cefalea. Metastasis cerebrales. Cáncer sistémico.*

Introduction

The lifetime possibility of being diagnosed with an invasive cancer is around 40%[1]. Approximately 10-30% of patients with cancer will develop brain metastases (BM) at some point during their disease. However, the true incidence of BM might be higher, with autopsy studies suggesting an incidence of up to 40%[2]. The prognosis of patients who develop BM is usually poor, with a median overall survival of 12 months after being diagnosed with BM[3].

Headache is the most prevalent neurological symptom experienced by almost everyone; the actual percentage of the adult population with an active headache is around 47%[4]. The principal general cause is a primary headache, accounting for at least 80% of cases[5]. Secondary causes of headache should be considered and excluded if the headache does not fulfill corresponding criteria established by the International classification of headache disorders-3 (ICHD-3)[6]; or if the headache presents with any simultaneous red flag, especially those abbreviated as systemic symptoms/signs and disease, neurologic symptoms or signs, onset sudden, onset after the age of 40 years, and change of headache pattern) which includes having co-occurrent or previous cancer[5,7]. Characteristics of headache often provide valuable information about the underlying etiology; therefore, the type of headache, onset, intensity, accompanying nausea/vomiting, location, temporality, exacerbation with Valsalva maneuver or cough, modifiers (such as position or Valsalva maneuver), or any other simultaneous neurologic symptom or sign should continuously be assessed[8,9]. Prior studies have described headache characteristics in patients with brain tumors[10-14], also known as brain tumor-associated headache[12]; however, studies that report headache characteristics or accompanying symptoms or signs in patients with systemic cancer who are diagnosed with BM are scantly found.

The present study aimed to measure the association of headache characteristics and accompanying neurologic signs and symptoms with the diagnosis of BM in patients with systemic cancer.

Materials and methods

A retrospective observational study at a single center included patients with pathologically confirmed systemic cancer sent by their primary oncologist specialist for the evaluation by the neuro-oncology (NeOn) unit due to headache. Patients with a primary central nervous system (CNS) or hematologic malignancy were excluded from the study. To determine if patients presented with BM, most patients had a magnetic resonance imaging (MRI) of the brain done. The NeOn followed patients not evaluated by an MRI for at least 1 year. BM were excluded based on MRI results or if clinical/neurological deterioration was not seen during the 1st year after the NeOn consultation.

We used the following definitions: synchronic tumor, more than one diagnosed active systemic malignant neoplasm (i.e., breast cancer and sarcoma). A visual complaint was determined when papilledema, diplopia, ptosis, or decreased visual acuity were present. Valsalva maneuver exacerbation if patients reported aggravation of the headache while performing a physical effort (i.e., during defecation, urination, or coughing). Headache intensity was measured with the visual analog scale (VAS) as rated by the patients.

Statistical analysis

We present continuous variables as either mean plus standard deviation or median with interquartile range. For nominal variables, we use numbers (No.) and percentages. Simple logistic regression analysis (simple logit) was used to measure the association of variables with BM; odds ratio (OR) and its 95% confidence interval (95% CI)

were calculated, a $p < 0.05$ was used to determine a significant association. A logistic regression (multiple logits) model was built from variables significantly associated with BM in the simple logit. The statistical analyses used the Statistical Package for the Social Sciences (SPSS) version 25.0 (SPSS Inc, Chicago, IL. USA).

Ethics approval

This is an observational study authorized by the Research Scientific and Ethical Committees (INCAN/Rev/07/12).

Results

From 1,248 patients sent for NeOn consultation due to headache, 519 were diagnosed with a hematologic malignancy and 154 with a primary CNS tumor and thus excluded; therefore, we present the characteristics of 572 patients with cancer who complained of headache, of which 216 (38%) were diagnosed with BM.

The mean age at NeOn evaluation was 49.7 ± 13.1 years. Female gender was more prevalent (86%); the primary systemic tumor was breast in 261 patients (46%), gynecologic (cervix-uteri, ovarian, and endometrial) in 91 (16%), head and neck in 51 (9%), lung in 50 (9%), urologic in 34 (6%), skin (including melanoma) in 4%, other (i.e., bone, soft tissue, and primary undetermined) in 4%, synchronic (more than two primary sites) in 4%, and gastrointestinal in 3%.

Headache characteristics

Mean headache intensity was VAS 7 ± 2, most patients n, 477 (83%), started with a headache after cancer was diagnosed, and the remaining presented with a headache before cancer was diagnosed as a primary headache that suffered modifications or had changed during time. Localization of headache was generalized in 201 (35%), hemicranial in 126 (22%), occipital or located at the Hindhead in 76 (13%), and the rest had either mixed location, periocular, or other. Headache was described as oppressive in 163 (28%), pulsating in 102 (18%), lancinating in 73 (13%), explosive in 44 (8%), and mixed forms or poorly described in the remaining patients. Nausea was present in 134 (23%), nausea and vomiting in 111 (19%), and vomiting in 64 (11%). Headache timing was nocturnal or during sleep in 125 (22%), matutinal or during the morning in 69 (12%), in the evening in 41 (7%), during all day in 9 (2%), and the remaining had non-specific or variable timing. Headache worsened with Valsalva in 126 (22%) and with changes in position in 126 (22%). After multiple logits, headache characteristics that were associated with BM were: male gender OR = 1.97 (95% CI 1.09-0.59) $p = 0.025$, a headache starting after cancer diagnosis OR = 21 (95% CI 6-71) $p < 0.001$, generalized location OR = 0.34 (95% CI 0.20-0.57) $p < 0.001$, oppressive type OR = 1.9 (95% CI 1.1-2.2) $p = 0.017$, presence of vomit with nausea OR = 7.82 (95% CI 3.8-16.1) $p < 0.001$ or without nausea OR = 5.8 (95% CI 2.7-12.6) $p < 0.001$, and exacerbation of headache with changes in position OR = 2.2 (95% CI 1.3-3.9) $p = 0.006$. Table 1 describes headache characteristics and their association with BM.

Neurologic signs

Headache presented as a single neurologic complaint in 288 (50%) patients; another neurologic sign was seen in 284 (50%), being the most common altered mental status in 105 (18%), a visual complaint in 86 (15%), focal motor weakness 70 (12%), seizures in 65 (11%), a focal sensitive complaint in 46 (8%), ataxia in 43 (8%), vertigo in 35 (6%), vertebral or radicular pain in 33 (6%), cranial neuropathy in 16 (3%), a cognitive deficit in 16 (3%), speech alterations in 13 (2%), and abnormal movements in 9 (2%). After multiple logits, having another neurologic complaint – other that headache – was associated with the diagnosis in BM (OR = 6.1 [95% CI 2.1-17.3] $p = 0.001$); mainly ataxia OR = 19.8 (95% CI 4.9-79) $p < 0.001$, visual complaint OR = 15.6 (95% CI 5.5-44.1) $p < 0.001$, altered mental status OR = 15.4 (95% CI 5.7-42) $p < 0.001$, seizures OR = 15.0 (95% CI 4.8-46.8) $p < 0.001$, focal motor weakness OR = 11.7 (95% CI 3.9-34.6) $p < 0.001$, cognitive complaint OR = 7.7 (95% CI 1.2-50.9) $p = 0.034$, and vertigo OR = 3.8 (95% CI 1.2-12.5) $p = 0.025$. Table 2 describes neurologic complaints and their associations with the diagnosis of BM.

Discussion

In a cohort of patients with systemic cancer sent for NeOn consultation due to headache, BM were found in 38%; clinical characteristics associated with a higher risk of BM were age < 65 years, male gender, a headache starting after a cancer diagnosis, oppressive type, and the presence of vomiting; having an exacerbation of headache with changes in position and generalized location correlated with a lower risk of BM. In addition, more than one neurologic complaint (other than a headache) was associated with a higher risk of BM,

Table 1. Simple and multiple logistic regression analyses for the association of headache characteristics with brain metastases (BM) diagnosis in 572 patients with systemic cancer

Variable (No. with the condition)	No. patients with BM (%) n = 216 (38%)	Simple logit		Multiple logit	
		p-value	OR (95% CI)	p-vlaue	OR (95% CI)
Female (n = 494) Male (n = 78)	173 (35) 43 (55)	0.001	Reference 2.28 (1.40-3.69)	0.025	Reference 1.97 (1.09-3.59)
Age < 65 years (n = 498) ≥ 65 years (n = 74)	 196 (39) 20 (27)	 0.043	 1.75 (1.01-3.01) Reference	 0.062	 1.80 (0.97-3.35) Reference
Intensity, median = ± IQR (n = 572) BM (n = 216) No BM (n = 356)	7 (2-9) 7 (5-9) 8 (6-9)	0.239	1.04 (0.97-1.12)	-	-
Headache started After cancer (n = 477) Before cancer (n = 95)	 213 (45) 3 (3)	 < 0.001	 24.7 (7.27-79.24) Reference	 < 0.001	 21.23 (6.26-71.0) Reference
Localization Hemi cranial (n = 126) Generalized (n = 201) Occipital/Hindhead (n = 76) Mixed/Other (n = 169)	 23 (18) 117 (58) 28 (37) 48 (28)	 0.045 <0.001 0.188 -	 1.77 (1.01-3.11) 0.28 (0.18-0.44) 0.68 (0.38-1.20) Reference	 0.435 < 0.001 0.533 -	 1.29 (0.67-2.46) 0.34 (0.20-0.57) 0.81 (0.42-1.56) Reference
Type Oppressive (n = 163) Pulsatile (n = 102) Lancinating (n = 73) Explosive (n = 44) Other (n = 190)	 47 (29) 31 (30) 35 (48) 12 (27) 91 (48)	 < 0.001 0.004 0.994 0.015 -	 2.26 (1.45-3.53) 2.10 (1.26-3.50) 0.99 (0.58-1.71) 2.45 (1.19-5.04) Reference	 0.017 0.103 0.792 0.151 -	 1.90 (1.12-3.23) 1.67 (0.90-3.09) 1.09 (0.57-2.08) 1.94 (0.78-4.79) Reference
Nausea and vomiting (n = 111) Nausea only (n = 134) Vomiting only (n = 64) None (n = 263)	64 (58) 39 (29) 46 (72) 67 (26)	< 0.001 0.062 < 0.001 -	7.47 (4.05-13.7) 1.87 (0.96-3.64) 6.22 (3.2-12.04) Reference	< 0.001 0.110 < 0.001 -	7.82 (3.78-16.17) 1.92 (0.86-4.27) 5.78 (2.65-12.60) Reference
Timing Morning (n = 69) Evening (n = 41) Night/sleep (n = 125) All day (n = 9) Mixed/no preference (n = 328)	 22 (32) 6 (15) 33 (26) 2 (22) 216 (38)	 0.167 0.558 0.577 0.787 -	 0.32 (0.06-1.59) 0.61 (0.11-3.18) 1.66 (0.27-10.02) 0.79 (0.15-4.02) Reference	-	-
Worsens with Valsalva (n = 126) Does not (n = 446)	40 (32) 176 (40)	0.116	Reference 1.40 (0.92-2.13)	-	-
Worsens with changes in position (n = 126) Does not (n = 446)	28 (22) 188 (42)	< 0.001	Reference 2.55 (1.61-4.04)	0.006	Reference 2.20 (1.25-3.85)

IQR: Interquartile range.

especially if patients had ataxia, visual complaint, altered mental status, seizures, focal motor weakness, and vertigo.

Headache is a well-recognized red flag in patients with cancer for a secondary cause, such as BM, and should permanently be excluded[15]. Headache is the most frequent neurological symptom associated with brain tumors (both primary or metastatic)[16]. Previous studies have reported a prevalence of headache in 8-71% of patients with brain tumors[9,10,12,17-21]. They have also reported the so-called "classic" brain tumor headache characteristics (described as severe, worse in the morning, with nausea and vomiting) to be uncommon, similar to our findings. On the other hand, following our results, other simultaneous neurological symptoms have been consistently associated with BM[12,13,17,19]. In our study, 73% of patients with a headache diagnosed with BM had another accompanying neurological symptom.

Headache in patients with cancer does not always mean having a BM; differential diagnoses include primary

Table 2. Simple and multiple logistic regression analyses for the association of accompanying neurologic signs or symptoms with brain metastases in 572 patients with headache and systemic cancer

Variable (No. with the condition)	No. patients with BM (%) n = 216 (38%)	Simple logit		Multiple logit	
		p-value	OR (95% CI)	p-value	OR (95% CI)
Only headache (n = 288) Headache+another symptom (n = 284)	9 (3) 207 (73)	< 0.0001	83.33 (40.03-170.09) Reference	0.001	6.08 (2.13-17.34) Reference
Altered mental status (n = 105) Absent (n = 467)	96 (91) 120 (26)	< 0.0001	30.84 (15.10-62.99) Reference	< 0.001	15.42 (5.66-42.00) Reference
Visual complaint (n = 86) Absent (n = 486)	78 (91) 138 (28)	< 0.001	24.58 (11.56-52.35) Reference	< 0.001	15.60 (5.52-44.10) Reference
Focal motor weakness (n = 70) Absent (n = 502)	63 (90) 153 (31)	< 0.001	20.52 (9.19-45.85) Reference	< 0.001	11.67 (3.93-34.61) Reference
Seizures (n = 65) Absent (n = 507)	59 (91) 157 (31)	< 0.001	21.92 (9.27-51.84) Reference	< 0.001	15.01 (4.81-46.78) Reference
Focal sensitive complaint (n = 46) Absent (n = 526)	27 (59) 189 (36)	0.003	2.53 (1.37-4.67) Reference	0.921	0.94 (0.32-2.75) Reference
Ataxia (n = 43) Absent (n = 529)	40 (93) 176 (33)	< 0.001	26.74 (8.15-87.65) Reference	< 0.001	19.79 (4.91-79.71) Reference
Vertigo (n = 35) Absent (n = 537)	26 (74) 190 (35)	< 0.001	5.27 (2.42-11.49) Reference	0.025	3.85 (1.18-12.52) Reference
Vertebral/radicular pain (n = 33) Absent (n = 539)	12 (36) 204 (38)	0.864	0.93 (0.45-1.94) Reference	-	-
Cranial neuropathy (n = 16) Absent (n = 556)	12 (75) 204 (37)	0.005	5.17 (1.64-16.26) Reference	0.054	4.57 (0.97-21.51) Reference
Cognitive complaint (n = 16) Absent (n = 556)	14 (88) 202 (36)	0.001	12.26 (2.76-54.52) Reference	0.034	7.71 (1.16-50.96) Reference
Speech disorder (n = 13) Absent (n = 559)	12 (92) 204 (37)	0.004	20.88 (2.69-161.76) Reference	0.866	0.81 (0.07-9.00) Reference
Abnormal movements (n = 9) Absent (n = 563)	2 (22) 214 (38)	0.344	0.46 (0.96-2.26) Reference	-	-

intracranial tumors (i.e., pituitary tumors, gliomas, and meningiomas)[21], neuroinfections, vascular disease, radiotherapy, complications of systemic treatments, steroid use or withdrawal, intracranial hypertension, lumbar puncture, aseptic meningitis, systemic hypertension, and finally, primary headaches[15,16,21]. In addition, the pathogenesis of brain tumor headaches varies and has been reviewed elsewhere[9,22].

One of the essential strengths of our study is that we looked directly for associations between headache characteristics and the presence of BM in numerous cohorts and compared them with those without BM. Previous studies[10,17,18] have only reported frequencies or studied a smaller sample size[23]; furthermore, it is not unusual to find many physicians and medical literature recognizing specific headache characteristics as associated with a brain tumor without checked bases. In future studies, this research can be used to verify the clinical significance of the headache features that are linked to BM.

An individualized validation for each cancer-specific site (i.e., melanoma, lung, and breast cancer) would be ideal, and multicenter prospective studies are encouraged to confirm our findings. The retrospective design, a referral bias, and a selection bias should be considered, for the study was done in patients treated at a single center, and the decision of referring patients for NeOn evaluation was determined by their primary treating physician (medical-, radio-, or surgical oncologist), according to their clinical judgment.

We did not classify the type of headache as others have done or attempted to do so because the criteria for primary headaches exclude the presence of secondary causes (i.e., not better accounted for another ICHD-3

diagnosis and other reasons have been excluded)[6,14]. The ICHD-3 has defined a 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 causality was demonstrated by one or more of the following: (a) the headache symptom developed in temporal relation to the cranial neoplasm or led to its discovery; (b) the headache significantly emerged in parallel with the worsening of the intracranial neoplasm; (c) the headache significantly improved in temporal relation to the success of treatment of the intracranial neoplasm; and (d) another ICHD-3 diagnosis does not better explain it"[6,22]. If our current results are prospectively confirmed, other clinical characteristics might be considered an extra item for the following classification.

Finally, all of our patients were seen in the outpatient setting or during hospitalization; the emergency room approach to headaches ought to be managed according to best-practice evidence[7,24,25].

Conclusion

Headache in patients with cancer is a warning sign, especially if it begins after a cancer diagnosis, male gender, and age < 65 years. The attending team should consider headache characteristics, accompanying symptoms, and signs to assess their risk of being diagnosed with BM as the etiology of their headache.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data, and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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