Brain tumors and promptness in primary care diagnosis

Tumores cerebrales y prontitud en el diagnóstico en atención primaria

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Abstract

Introduction: cancer diagnosis is usually made in secondary care; primary diagnosis is vital.
Purpose: To examine how different symptoms and patient demographics predict variations in time to brain tumor diagnosis.
Methods: A retrospective secondary analysis of brain tumor cases in 20 primary care practices were performed.
Results: The most common symptom domain was focal neurology, including stroke (33.2%), followed by episodic seizures:“attacks, fainting or fall” (20.8%).
Conclusions: General practitioners currently face a diagnostic challenge in deciding whether to refer patients with headaches and memory problems.
Keywords: brain tumor, primary care, general practitioners, headache, neurological symptoms source: DeCS
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Resumen
Introducción:El diagnóstico de cáncer generalmente se realiza en atención secundaria, el diagnóstico primario es vital.
Objetivo: Examinar cómo los diferentes síntomas y la demografía de los pacientes predicen las variaciones en el tiempo hasta el diagnóstico del tumor cerebral.
Método: Se realizó un análisis secundario retrospectivo de casos de tumores cerebrales en 20 prácticas de atención primaria
Resultados: El dominio de síntomas más común fue la neurología focal, incluido el accidente cerebrovascular (33,2 %), seguido de los ataques episódicos: “ataques, desmayos o caídas” (20,8 %).
Conclusiones:Los médicos de cabecera actualmente se enfrentan a un desafío de diagnóstico al decidir si derivar a los

pacientes con dolores de cabeza y problemas de memoria.

Palabras clave: tumor cerebral, atención primaria, médicos generales, dolor de cabeza , síntomas neurológicos
fuente: DeCS

Introduction

The incidence of brain tumors is low; age-adjusted incidence rates for all gliomas range from 4.7 to 5.7 per 100,000 persons. This means that brain tumor diagnosis is very rare in primary care populations. While a cancer diagnosis is usually made in secondary care, most patients will have seen their primary care physician prior to diagnosis(1). In addition, patients may present with a wide range of symptoms that may be common (e.g., headache), non-threatening, or may be considered part of a normal aging process (e.g., memory loss). The lack of specificity of these symptoms creates a diagnostic challenge for all clinicians. Current guidelines recommend that a specialist should see all patients with suspected central nervous system (CNS) tumors within two weeks of referral from their primary care physician; despite the introduction of this guideline, there appears to have been little improvement in the diagnostic interval (the time from the first presentation with symptoms to diagnosis) over the past decade(2). The most recent figures show that only 1% of cases with a suspected brain tumor are diagnosed through the 2-week ‘suspected cancer’ waiting process, 17% are GP referrals through the usual routes, and 58% are diagnosed following an accident and emergency care(3).

Several studies have examined case series of patients with brain tumors and quantified the frequency of the most common presenting symptoms(4); in some cases, deriving predictive values by comparing this with age- and sex-matched control patients in primary care. A systematic review(5) found that all symptoms generally had low positive predictive values for brain tumors, apart from new-onset epilepsy. However, few studies have investigated how symptoms may influence the timing of diagnosis. One study previously found that about one-third (35.2 %) of patients with brain tumors took 15 days or more to see their primary care physician and 21.4 % of cases required three or more consultations before referral compared with 17.9 % for all cancers or just 2.9 % for breast cancer patients(6).

This study examines whether different clinical presentations are associated with variations in the patient’s pathway to diagnosis and where future interventions might best be focused on to reduce diagnostic delay and improve patient prognosis.

Method

A retrospective secondary analysis of brain tumor cases in 20 primary care practices in the city of Ambato was conducted from 2010 to 2020. This study was approved by the Universidad Regional Autónoma de Los Andes (UNIANDES).

Only patients with a confirmed brain tumor diagnosis were selected for this analysis. In addition, three other related outcomes were observed that may indicate a suboptimal referral interval: (i) whether the patient attended primary care three or more times prior to referral and (ii) the GP’s response to the following questions (a) ‘Did prompt access to investigations alter your management of this case?’ and (b) ‘Were there any avoidable delays in this patient’s journey?’

Primary care physicians or professionals collect information from patients’ medical records. In addition, the following covariateswere also examined: gender, age group (<60, 60-70, >70 years), whether the patient had communication problems, whether the patient was homebound, and whether the GP ordered investigations prior to referral, where patients presented for the first time and which specialist was chosen for a referral.

The median (interquartile range) time to diagnosis (in days) was calculated according to the patient, referral, specialist, and pathway intervals by symptom domains and other factors. Multivariable Odds Ratios (OR) are based on the imputed data set to maximize statistical power, given the relatively small sample size. Database and statistical processing of the data were performed and analyzed in SPSS 26 statistical software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used for the results collection, presentation and interpretation.

Results

There were 226 patients (96.6%) with information on presenting symptoms of 234 cases of brain tumors. The age distribution was bimodal (young and old), with approximately equal numbers of males and females. The most common symptom domain was focal neurology, including stroke (33.2 %), followed by episodic seizures: "fits, fainting or fall" (20.8 %) and headache (20.8 %). About 30% of the cases had had three or more consultations before referral. In about one-third of the cases, physicians considered or were unsure whether there were avoidable delays. About 20% of GPs felt that prompt investigation access would have been helpful.

The median (interquartile range) of the pathway interval was 24 days (7-65 days) (Table 1). Younger patients (< 60 years) had longer pathway delays. There were marked variations in pathway interval by symptom domain. The shortest time was observed for episodic seizures-"fits, fainting or fall" (10 days), while the longest interval was observed for memory loss (62 days). Patients who had investigations before referral to specialty care had a longer pathway interval.

Table 1. The median and interquartile range of time to diagnosis (days) by sociodemographic characteristics of patients with a brain tumor.

Variable	Time to diagnosis							
	Patientinterval		Primary care interval		Interval toSpecialist		Routeinterval	
	Mean (n)	InterquartileRange	Mean (n)	InterquartileRange	Mean (n)	InterquartileRange	Mean (n)	InterquartileRange
Age group								
<60	5.5	0–25,5	3	0–31,5	6	0–19	25.5	8–81
60-69	8	1–26	2	0–6	2	0–12.5	20.5	7–63
>60	5	0–15,5	1	0–15	7	0–24	22	7–54
Sex								
Female	5	0–21	1.5	0–13,5	4	0–15	25	7–60,5
Male	8	1–26,5	2	0–15	6	0–17	24	8–66
Homebound								
No	7	0–29	1	0–11	6	0–17	25	7–77
Yes	3	0–8	4	0–24	4.5	0–11	15	6–44

Symptoms								
Headache	9	2–45	6	0–30	2	0–11	30	11–86
just a headache	10	4–101	17.5	5–64	2	0–10	61	20–197
Headache in addition	6	2–18,5	4	0–24	2	0–15	223	7–60
Behavioral/cognitive	14	3–62	4	0–16	9	0–19	39	13–90
Confusion	16.5	7–31	1.5	0–6	2.5	0–16	18.5	4.5–41
Memory	14	2–62	5	0–21	11	2–21	62	35–95
focal neurology	5	0–14	0	0–7.5	9	0–24	21	7–61
Seizures, blackoutsorfalls	3.5	0–30	0	0–5	0	0–11	10	0–42
nonspecificneurological	12.5	0–28	15	0–35	8	1–17	50	43–65
Other/nonspecific	3	0–22	3	0–80	4.5	0–7	16	7–66
Investigation prior toreferral								
No	5	0–18	0	0–4	3.5	0–15	14.5	5–50
Yes	13	1–31	11	4–43	7	0–19	55.5	30–110
Reference type								
Emergency	4.5	0–18	0	0–6	0	0–3	14	6–39
Notreferredbypractice	10	0–22	2	0–6.5	0	0–7	7	0–23
Routine	6	0–33	7	0–80	24.5	12,5–53,5	81	50–141
To which specialist to refer								
Emergencies	5	0–10	0	0–4	0	0–7	11	7–25
Neurosurgery /Neurology	8.5	1–26	5	0–33	8	1–19	43.5	10–83
Internal Medicine/Ictus/Miscellaneous	5	0–29	1	0–11	3	0–19	27	8–82

Source: statisticalanalysis, $p \leq 0.05$

Compared to 'seizures, fainting or falls', headache and non-specific neurological groups showed a significantly elevated OR for shunting (OR = 6.47, 95 % CI = 1.22, 34.3 and OR = 11.9, 95 % CI = 1.82, 77.8, respectively). When looking at the subgroups, headache only (i.e., headache without any other reported characteristics) and memory only, they showed larger ORs for the total pathway interval (OR = 4.11, 95 % CI = 1,10, 15.5 and OR = 4.82, 95 % CI = 1.15, 20.1, respectively), which was mainly due to the slower primary care interval (OR = 11.8, 95 % CI = 1.88, 73.9 and OR = 10.9, 95 % CI = 1.79, 66.1, respectively). GP diagnostic investigations prior to referral were also associated with slower referral and slower overall pathways. As expected, routinely referred patients had longer primary care and specialist delays, and accident and emergency referrals had shorter intervals between patients, specialists, and pathways.

Both headache and behavioral/cognitive changes and nonspecific symptoms were associated with at least three or more presentations prior to referral and this was most marked only for headache (OR = 7.92, 95 % CI = 1.80, 34.8) and memory complaints (OR = 6.09, 95 % CI = 1.30, 28.6). GPs felt quicker access to investigations would have helped with headaches and focal neurological symptoms. GPs retrospectively reported that there were avoidable delays for patients presenting with headache alone on the patient journey (OR = 3.64, 95 % CI = 0.83, 15.9), but this was consistent with chance.

Discussion

Marked variability in the time was found from symptom onset to the first visit to a specialist for patients with brain tumors, depending on their symptoms. Overall, the median time from symptom presentation to being seen by a specialist was <4 weeks. Patients presenting with headaches, behavioral/cognitive changes or other nonspecific symptoms saw their primary care physician more frequently before referral; headache alone and memory loss are associated with much slower patient processing, primarily due to delays in referral to a specialist (secondary care).

Most previous diagnostic pathway studies have focused on specific tumor types, e.g., vestibular schwannoma, intradural spinal cord tumors, pituitary adenomas, acoustic neuromas, central nervous system lymphomas, or intracranial tumors[7,8]. Similarly, nonspecific or more subtle features, such as personality changes, were associated with late remission in a case series of 58 patients with primary central nervous system lymphoma. Retrospective interviews with patients and family members may reveal a history of more subtle problems, such as cognitive or personality changes, although the patient may be unaware of these symptoms[9].

The positive predictive value of headache in adult patients with brain tumors is low (0.09% overall, but 0.12% in persons aged 60-69 years) compared with new-onset seizures (1.2%)[10]. Because headache is a common complaint, it is difficult for general practitioners and physicians to differentiate less serious causes from headaches secondary to a brain tumor. Headaches associated with brain tumors are often of the “tension” type or mimic migraine[11] and the best clues are increased frequency and severity and characteristics of the headache (e.g., worsening with coughing or bending over, nighttime headaches, or headaches on awakening). The development of additional symptoms, e.g., focal neurology or signs (papilledema), will strongly support the diagnosis. This underscores the importance of GPs looking for additional symptoms, such as behavioral/cognitive changes if they are unsure whether a patient with a headache requires investigations or referral to a specialist. The use of simple cognitive screening tests, such as semantic verbal fluency, can help. This requires assessment of how many animals the patient can name in one minute and has previously been shown to be worse in patients with brain tumors whose initial presenting symptom was headache/headache and other ‘[12,13].

The study is generalizable to other high-income healthcare settings, as cases were identified consecutively from primary care without any selection by specialized units. Most studies do not prospectively collect data on patient delay, so they cannot disentangle the patient pathway into all its constituent components. However, we were forced to group several symptoms into domains to achieve sufficient power due to the sample size[14]. Headaches associated with “nausea” and “vomiting” (N&V) were included in the headache and other groups due to the lack of qualifying information in the available data. Ideally, though, there would be a distinction between N&V observed in common conditions such as migraine and “atypical” or “red flag” N&V (such as N&V confined to early morning or bending over) that alert the primary care physician to the possibility of serious pathologies, such as a brain tumor[15]. It is not observed how presentation and delay were associated with brain tumor type as we did not have data on specific pathology, size, and location. This would be of interest as it would also be associated with management and prognosis.

Interestingly, GPs felt quicker access to investigations such as neuroimaging would have helped, particularly for less specific symptoms such as headaches [16,17]. This important question needs to be analyzed in terms of cost-effectiveness given the potentially large number of patients who will have a normal scan. Current National Institute for Health and Care Excellence (NICE) guidance states that ‘Consider urgent direct access brain MRI (or CT scan if MRI is contraindicated) (to be performed within two weeks) to assess for brain or central nervous system cancer in adults with progressive subacute loss of central neurological function[18]. Patients with an only headache or simple memory loss would not be considered to meet these criteria. In addition, there is an implicit assumption that a reduction in the diagnostic interval for patients presenting with headaches and memory loss would result in improved clinical outcomes, which may or may not be true[19,20]. Future work should examine whether geographic areas with ready access to neuroimaging have reduced diagnostic delay and whether this translates into patient management, morbidity, and survival differences.

Conclusions

While many patients with brain tumors are diagnosed quickly, primary care physicians and other clinicians currently face a diagnostic challenge in deciding whether to refer patients with headaches and memory problems. Future work should identify whether additional features or other simple, inexpensive tests can be administered in primary care that could help reduce the time to diagnosis in these patients.

References

1. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a «state of the science» review. Neuro Oncol [Internet]. julio de 2014 [citado 18 de julio de 2022];16(7):896-913. Disponible en: https://pubmed.ncbi.nlm.nih.gov/24842956/
2. Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, et al. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. Br J Cancer [Internet]. 27 de marzo de 2012 [citado 21 de julio de 2022];106(7):1262-7. Disponible en: https://pubmed.ncbi.nlm.nih.gov/22415239/
3. Hamdan A, Mitchell P. The two-week wait guideline for suspected CNS tumours: a decade analysis. Br J Neurosurg [Internet]. octubre de 2013 [citado 22 de julio de

2022];27(5):642-5. Disponible en: https://pubmed.ncbi.nlm.nih.gov/23472626/

4. Ozawa M, Brennan PM, Zienius K, Kurian KM, Hollingworth W, Weller D, et al. The usefulness of symptoms alone or combined for general practitioners in considering the diagnosis of a brain tumour: a case-control study using the clinical practice research database (CPRD) (2000-2014). BMJ Open [Internet]. 30 de agosto de 2019 [citado 21 de julio de 2022];9(8):e029686. Disponible en: https://pubmed.ncbi.nlm.nih.gov/31471440/
5. Schmidt-Hansen M, Berendse S, Hamilton W. Symptomatic diagnosis of cancer of the brain and central nervous system in primary care: a systematic review. FamPract [Internet]. diciembre de 2015 [citado 23 de julio de 2022];32(6):618-23. Disponible en: https://pubmed.ncbi.nlm.nih.gov/26467645/
6. Keeble S, Abel GA, Saunders CL, McPhail S, Walter FM, Neal RD, et al. Variation in promptness of presentation among 10,297 patients subsequently diagnosed with one of 18 cancers: evidence from a National Audit of Cancer Diagnosis in Primary Care. Int J Cancer [Internet]. 1 de septiembre de 2014 [citado 27 de julio de 2022];135(5):1220-8. Disponible en: https://pubmed.ncbi.nlm.nih.gov/24515930/
7. Ambett R, Rupa V, Rajshekhar V. Analysis of causes for late presentation of Indian patients with vestibular schwannoma. J LaryngolOtol [Internet]. mayo de 2009 [citado 21 de julio de 2022];123(5):502-8. Disponible en: https://pubmed.ncbi.nlm.nih.gov/18808730/
8. Phi JH, Kim SK, Lee YA, Shin CH, Cheon JE, Kim IO, et al. Latency of intracranial germ cell tumors and diagnosis delay. ChildsNervSyst [Internet]. octubre de 2013 [citado 27 de julio de 2022];29(10):1871-81. Disponible en: https://pubmed.ncbi.nlm.nih.gov/23811803/
9. Sharma A, Fruth B, Barrera C, Farfour HN, Mrugala MM, Edwin MK, et al. How much time do we have? Longitudinal perception of prognosis in newly-diagnosed high grade glioma patients and caregivers compared to clinicians. J Neurooncol [Internet]. abril de 2021 [citado 27 de julio de 2022];152(2):313-23. Disponible en: https://pubmed.ncbi.nlm.nih.gov/33486637/
10. Grant R, Dowswell T, Tomlinson E, Brennan PM, Walter FM, Ben-Shlomo Y, et al. Interventions to reduce the time to diagnosis of brain tumours. Cochrane DatabaseSyst Rev [Internet]. 4 de septiembre de 2020 [citado 21 de julio de 2022];9:CD013564. Disponible en: https://pubmed.ncbi.nlm.nih.gov/32901926/
11. Hamilton W, Kernick D. Clinical features of primary brain tumours: a case-control study using electronic primary care records. Br J Gen Pract [Internet]. septiembre de 2007 [citado 27 de julio de 2022];57(542):695-9. Disponible en: https://pubmed.ncbi.nlm.nih.gov/17761056/
12. Kerrigan S, Erridge S, Liaquat I, Graham C, Grant R. Mental incapacity in patients undergoing neuro-oncologic treatment: a cross-sectional study. Neurology [Internet]. 5 de agosto de 2014 [citado 21 de julio de 2022];83(6):537-41. Disponible en: https://pubmed.ncbi.nlm.nih.gov/24991034/
13. Dommett RM, Pring H, Cargill J, Beynon P, Cameron A, Cox R, et al. Achieving a timely diagnosis for teenagers and young adults with cancer: the ACE «too young to get cancer?» study. BMC Cancer [Internet]. 24 de junio de 2019 [citado 18 de julio de 2022];19(1):616. Disponible en:

https://pubmed.ncbi.nlm.nih.gov/31234813/

14. Oronsky B, Reid TR, Oronsky A, Sandhu N, Knox SJ. A Review of Newly Diagnosed Glioblastoma. Front Oncol [Internet]. 2020 [citado 28 de julio de 2022];10:574012. Disponible en: https://pubmed.ncbi.nlm.nih.gov/33614476/
15. Day J, Gillespie DC, Rooney AG, Bulbeck HJ, Zienius K, Boele F, et al. Neurocognitive Deficits and Neurocognitive Rehabilitation in Adult Brain Tumors. CurrTreatOptions Neurol [Internet]. mayo de 2016 [citado 27 de julio de 2022];18(5):22. Disponible en: https://pubmed.ncbi.nlm.nih.gov/27044316/
16. Benamore RE, Wright D, Britton I. Is primary care access to CT brain examinations effective? Clin Radiol [Internet]. octubre de 2005 [citado 27 de julio de 2022];60(10):1083-9. Disponible en: https://pubmed.ncbi.nlm.nih.gov/16179168/
17. Carey MR, Callaghan BC, Kerber KA, Skolarus LE, Burke JF. Impact of early headache neuroimaging on time to malignant brain tumor diagnosis: A retrospective cohort study. PLoSOne [Internet]. 2019 [citado 18 de julio de 2022];14(2):e0211599. Disponible en: https://pubmed.ncbi.nlm.nih.gov/30707721/
18. Ceronie B, Hart T, Belete D, Ramani L, Bahra A. Isolated headache is not a reliable indicator for brain cancer: the 2-week wait pathway for suspected CNS malignancies. Clin Med (Lond) [Internet]. noviembre de 2021 [citado 23 de julio de 2022];21(6):e648-55. Disponible en: https://pubmed.ncbi.nlm.nih.gov/34862227/
19. Cerqua R, Balestrini S, Perozzi C, Cameriere V, Renzi S, Lagalla G, et al. Diagnostic delay and prognosis in primary central nervous system lymphoma compared with glioblastoma multiforme. Neurol Sci [Internet]. enero de 2016 [citado 21 de julio de 2022];37(1):23-9. Disponible en: https://pubmed.ncbi.nlm.nih.gov/26233232/
20. Peeters MCM, Dirven L, Koekkoek JAF, Gortmaker EG, Fritz L, Vos MJ, et al. Prediagnostic symptoms and signs of adult glioma: the patients' view. J Neurooncol [Internet]. enero de 2020 [citado 27 de julio de 2022];146(2):293-301. Disponible en: https://pubmed.ncbi.nlm.nih.gov/31894516/