Clinical features of primary brain tumours:

a case–control study using electronic primary care records

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ABSTRACT

Background

Around 4500 new primary brain tumours are diagnosed in the UK each year. Symptoms of these tumours have not previously been studied in primary care.

Aim

To identify and quantify the clinical features of brain tumours in primary care.

Design of study

Case–control study.

Setting

The General Practice Research Database, UK.

Method

A total of 3505 patients with primary brain tumours diagnosed between May 1988 and March 2006, and 17 173 controls, matched for age (to 1 year), sex, and general practice, were studied. Full medical records for 6 months before diagnosis were searched for reports of clinical features previously associated with brain tumours. Odds ratios were calculated for variables independently associated with cancer, using conditional logistic regression, as were the positive predictive values for patients consulting in primary care.

Results

Seven features were associated with brain tumours before diagnosis. Positive predictive values against a background risk of 0.013% were: new-onset seizure, 1.2% (95% confidence interval [CI] = 1.0 to 1.4); weakness (as a symptom), 3.0% (95% CI = 1.7 to 4.9); headache, 0.09% (95% CI = 0.08 to 0.10); confusion, 0.20% (95% CI = 0.16 to 0.24); memory loss, 0.036% (95% CI = 0.026 to 0.052); visual disorder, 0.035% (95% CI = 0.025 to 0.051); and the physical sign of motor loss on examination, 0.026% (95% CI = 0.024 to 0.030); all $P<0.001$, except for visual disorder, $P = 0.005$. In a sub-analysis by age, the maximum risk of a brain tumour with headache or new-onset seizures was found in the age group 60–69 years (0.13% and 2.3% respectively).

Conclusion

The findings suggest that isolated headache presented to primary care has too small a risk of an underlying brain tumour to warrant investigation at presentation. However, new-onset seizures should be investigated.

Keywords

brain tumours; diagnosis; primary health care.

INTRODUCTION

Primary brain tumours account for around 2% of all new tumours in the UK, with over 4500 new diagnoses each year and an overall annual incidence of 7 per 100 000. They are more common in males and with increasing age. Most malignant brain tumours are fatal, but slower-growing tumours may allow survival for some years. Approximately 30% of tumours are benign, the most common being meningiomas. Other rarer tumours arise from local cell types, such as the pituitary or acoustic nerve. Secondary brain tumours are more common than primary ones, but in most patients the primary cancer has already been diagnosed, although a small proportion of patients first present with cerebral metastases.[1]

The symptoms of primary brain tumours have only been described in secondary care series. These have been mainly retrospective studies with a potential for recall bias. Up to 70% of patients have a headache during the course of their illness, particularly in the final stages of their disease; however, this is broadly the same as the population incidence of headache.[2] The incidence of headache at the time of diagnosis is between 23% and 56%; however, all these figures vary with the clinical setting, and may have been affected by recall bias.[2–4] Headache as a first and isolated presentation of brain tumours is much rarer: it is reported in 2–16% of patients.[5,6]

Epilepsy is also a feature of some brain tumours, particularly in younger patients, and may precede

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How this fits in

Brain tumours are rare, and very few primary care clinicians gain experience in their diagnosis. Several symptoms have been described from secondary care series, but no research has examined symptom reporting in primary care. This study describes the symptoms recorded in primary care notes before brain tumours were diagnosed. Although headache was one of the symptoms associated with brain tumours, the risk of an underlying tumour was very small. This supports clinicians who deem brain scanning unnecessary for uncomplicated headache.

tumour diagnosis by years.[7,8] Around 9% of patients with brain tumours have a preceding hospital admission with epilepsy.[7] In two studies, an underlying tumour was identified in 6–7% of patients attending tertiary care with new-onset epilepsy.[9–11] Higher figures have been reported in studies which included metastatic tumours.[12] However, current guidance does not recommend routine neuroimaging of all patients with new-onset epilepsy: when a diagnosis of idiopathic generalised epilepsy has been made, it is suggested that imaging can be omitted.[13]

Other reported symptoms of brain tumours include confusion, dysphasia, hemiplegia, motor weakness, personality change, and memory loss.[14] The risk posed by these symptoms has not been quantified,[8] and all are much more commonly caused by conditions other than brain tumours. It is difficult for clinicians to decide when to investigate for a possible brain tumour[15] and this is particularly relevant in primary care, where symptoms such as headache are common and the risk of an underlying tumour is low. No study of the features of brain tumour has been performed previously in this setting. Therefore, this study sought to identify the clinical features of primary brain tumours presenting to primary care, and to calculate the approximate risk of brain tumour in patients for these symptoms.

METHOD

This was a case–control study using data from the General Practice Research Database (GPRD) in the UK. Doctors contributing to the GPRD, record full details of patient characteristics on their practice computers, including all consultations and diagnoses.

Box 1. Clinical features selected for study.

- Symptoms

  Confusion, headache, weakness, anxiety, depression, fatigue, vertigo, smoking, excess alcohol intake, personality change, memory loss, and disorders of smell or vision.

- Examination findings

  Motor loss, sensory loss, papilloedema, and abnormal visual fields.

- Diagnostic labels

  New-onset seizure, migraine, and upper respiratory tract infections.

Data are subject to thorough validation and stringent quality checks. Electronic records in the GPRD are regarded as high quality, and the database has been used in many epidemiological research studies.

Identification of cases and controls

A list of 112 brain tumour codes was assembled from the library of codes and categorised into benign (n = 27, mostly meningiomas) and malignant tumours (n = 85). One code read simply 'brain tumour.' Tumours with this code were assumed to be malignant, unless subsequent records contained only benign tumour codes. GPRD staff identified all 3549 patients aged 18 years or over with a brain tumour diagnosed between May 1988 and March 2006, and with at least 2 years of data before the first tumour code (the index date). For each case, all potential controls matched to the same practice and sex, and within 1 year of age of the case were identified: seven were selected from these using a computer-generated random sequence.

Cases and controls were only used if they had consulted at least once in the 6 months before the index date. This eliminated any patients erroneously registered with the participating practices (so-called 'ghosts') and also allowed calculation of positive predictive values (PPVs) for patients who actually consulted in primary care. Controls were excluded if they previously had a brain tumour.

Selection of clinical features likely to predict primary tumour

Libraries of codes for clinical variables previously described with brain tumours were assembled (Box 1). Occurrences of these variables in the 6 months before the index date in cases and controls were identified. Variables were retained only if they occurred in at least 1% of cases or controls (in practice, this was always cases). Re-consultations with the same symptom were also retained if the subsequent symptom was also present in 1% or more cases or controls. No restriction was placed on reporting of the variable before the 6 month period of study, except for seizures which were only used if the patient had no previous seizure or anticonvulsant therapy code in their records.

Identification of independent associations with tumours

Differences between cases and controls were analysed using conditional logistic regression. Variables associated with tumours in univariable analyses with $P \leq 0.1$ were entered into the multivariable analyses. This was performed in stages, first collecting similar variables together, such as those that could represent weakness. Using this approach, a final model was derived including all the variables independently associated with brain tumours. All

discarded variables were checked against the final model. Seven clinically plausible internal interactions were tested in the final model. Differences in variable reporting between benign and malignant tumours were tested by adding interaction terms between benign/malignant status and each variable, and assessing for significance by likelihood ratio testing.

Calculation of positive predictive values

PPV calculation was possible because all cases reported in the GPRD had been identified. PPVs for individual variables and for pairs of variables were calculated from likelihood ratio and the observed incidence of cancer during the study.[16] As four of 3459 cases and 6830 of 24 021 initially-selected controls had not consulted in primary care, PPVs were divided by 0.715 to give predictive values for the consulting population. Stratified analyses by 10-year age bands were performed for individual features, but these were not performed if any cell in the 2×2 table was <10.

Sample size calculations used an estimated 3500 cases. With this number, seven controls provided >99% power to identify a change in a rare variable from 1% prevalence in one group to 2% in the other, using a two-sided 5% α level. Analyses were performed using Stata (version 9).

RESULTS

After application of the exclusion criteria, the number of cases available for study was reduced from 3549 to 3505. Four cases had not consulted in primary care in the 6 months before diagnosis, and a further 40 cases had no matched controls who had consulted. The number of controls fell from 24 824 to 17 173. Of these, 803 were already in the study as cases (772 had been selected as a control for themselves, and 31 as a control for another case); 6830 had not consulted; and 18 were consulting controls to the four non-consulting cases. Of the 3505 cases, 2397 were recorded as malignant (with 948 gliomas and 280 astrocytomas recorded, the remainder being rare tumours, or simply recorded as a brain tumour), and 1108 were recorded as benign (1015 of these recorded as meningiomas). Demographic features of cases are shown in Table 1.

Univariable results for selected clinical features of cases and controls are shown in Table 2. The following features did not show any independent association with brain tumours: anxiety, depression, fatigue, migraine, sensory loss, upper respiratory tract infection, vertigo, smoking, or excess alcohol intake. Personality change, papilloedema, abnormal visual fields, and disorders of smell were reported on fewer than 10 occasions.

As PPVs are dependant on both the likelihood ratio and the prior odds, these were recalculated for each age band for headache and seizure. In both, the peak likelihood ratio and PPVs were in the age band 60–69 years, at 0.12% and 2.3% respectively. Calculation of PPVs for headache accompanied by a specific second symptom was not possible, as all combinations were reported too rarely by controls (no combination occurred more frequently than three times). Therefore, a PPV was calculated for headache plus any second symptom from Table 2. This combination was present in 99 cases and 16 controls, giving a PPV of 0.39% (95% confidence interval [CI] = 0.31 to 0.48).

Multivariable results are shown in Table 3. There was an antagonistic interaction term between weakness (as a symptom) and motor loss (as a sign or diagnosis), which reflects the overlap between these two variables. Two external interaction terms (testing whether a feature was more or less common in malignant tumours) were significant, with confusion more common in malignant tumours (interaction odds ratio [OR] = 2.9; 95% CI = 1.3 to 6.7; *P* = 0.013), and motor loss less common (interaction OR = 0.66; 95% CI = 0.46 to 0.94; *P* = 0.021).

Table 1. Demographics and incidence of brain tumours.

Age, years	Tumours, *n*	Malignant tumours, *n*	Females, *n* (%)	Person years in GPRD (*n* x 100 000)	Incidence of tumours[a]	Incidence of malignant tumours[a]
18–29	159	134	71 (45)	51.4	3.1	2.6
30–39	276	206	137 (50)	52.8	5.2	3.9
40–49	432	280	227 (53)	48.6	8.9	5.7
50–59	675	471	361 (53)	42.4	15.9	11.1
60–69	822	584	410 (50)	32.5	25.3	18.0
70–79	767	511	419 (55)	24.8	30.9	20.6
80–89	339	191	198 (58)	12.4	27.3	15.4
>90	35	20	21 (60)	2.4	14.6	8.3
Total	3505	2397	1844 (53)	267.3	13.1	9.0

GPRD = General Practice Research Database. [a]Incidence per 100 000 per year.

Table 2. Frequency of clinical features in cases and controls.

Variable	Cases, *n* (%), *n* = 3505	Controls, *n* (%), *n* = 24 021	LR (95% CI)	PPV[a] (95% CI)
Headache	362 (10.2)	261 (2.6)	6.9 (6.2 to 7.1)	0.09% (0.08 to 0.10)
Motor loss	308 (8.7)	731 (3.1)	21. (1.9 to 2.4)	0.026% (0.024 to 0.030)
New-onset seizure	154 (4.4)	8 (0.05)	96 (81 to 110)	1.2% (1.0 to 1.4)
Confusion	109 (3.1)	47 (0.2)	16 (13 to 19)	0.20% (0.16 to 0.24)
Weakness	95 (2.7)	42 (0.2)	11 (9.1 to 14)	0.14% (0.11 to 0.18)
Memory loss	37 (1.1)	64 (0.4)	2.9 (2.0 to 4.1)	0.036% (0.026 to 0.052)
Visual disorder	35 (1.0)	62 (0.3)	2.8 (2.0 to 4.1)	0.035% (0.025 to 0.051)

LR = likelihood ratio. [a]Positive predictive value in the consulting population.

Table 3. Multivariable analysis of the clinical features of brain tumours.

Variable	OR (95% CI)	*P*-value
Symptoms		
New-onset seizure	87.0 (42.0 to 180.0)	<0.001
Weakness	23.0 (7.1 to 77.0)	<0.001
Headache	6.7 (5.6 to 8.0)	<0.001
Confusion	11.0 (7.6 to 16.0)	<0.001
Memory loss	2.7 (1.7 to 4.2)	<0.001
Visual disorder	2.0 (1.2 to 3.3)	0.005
Physical sign		
Motor loss	1.8 (1.5 to 2.2)	<0.001
Interaction term		
Motor loss with weakness	0.2 (0.06 to 0.8)	0.025

OR = odds ratio.

DISCUSSION

Summary of main findings

This is the first study of the features of brain tumours from primary care. Most of the symptoms reported from secondary care series were highly significantly associated with cancer, both in univariable and in multivariable analyses. However, the risk of a brain tumour with each of the symptoms was very low, reflecting the low overall incidence of tumours. This explains the relatively high ORs in Table 3 (which show strong associations between symptoms and diagnosis of brain tumour), yet small PPVs in Table 2 (which reflect the strength of the association between the symptom and having a tumour, plus the background incidence of brain tumours). The exception to this was new-onset epilepsy, which had an overall risk of 1.2%, rising to 2.3% if the patient was >60 years of age. In contrast, the risk with headache presented to primary care was less than 1 in 1000. Even when a second symptom was present, the risk of a brain tumour only rose to 3.9 in 1000.

Strengths and limitations of the study

It is not known how accurate the tumour diagnoses were, but it is unlikely that such a serious diagnosis would be entered erroneously more than a few times. The incidence of malignant tumours is similar to the 2002 incidence in the UK, although without the male preponderance.[17] Some tumours were not classified as benign or malignant: a distinction that is less meaningful in relation to brain tumours than other tumours (a 'benign' brain tumour may cause death; a malignant brain tumour rarely, if ever, metastasizes). For the primary care clinician, this is not as important as it seems (although very important for the patient), as generalists will wish to identify all brain tumours, whatever their level of malignancy, and refer for further investigation.

The major limitation of the study is that it relies on doctors recording symptoms as well as diagnoses. It has always been a requirement of participation in the GPRD that diagnoses are recorded for every consultation. Symptom recording may not be as systematic, especially in the earlier years of the GPRD, when many practices maintained parallel written records. Furthermore, some of the variables studied are rather crude, reflecting the data source; for example, the headache code encompassed several different codes, and omitted potentially important factors, such as duration, type, and severity. GPs would routinely use these parameters in their assessments of the possibility of an underlying tumour. Under-recording of symptoms or signs may have meant that some features that are genuinely associated with brain tumours, such as papilloedema, were not identified in this study. For the calculation of PPVs, under-recording is less of a concern. PPV is derived from the likelihood ratio and the incidence; the latter is unlikely to be significantly subject to recording bias (especially as the incidence rates in this study were so close to published national rates). Likelihood ratios would be misleading if under-recording was systematically more prevalent in either cases or controls. There is no particular reason why this should be so, although it is possible that a spell of undiagnosed ill-health in cases before their diagnosis could lead to better symptom recording (and thus overestimation of PPVs).

Comparison with existing literature

The prevalence of most features in cases was lower than in previous studies,[8,18] except for the 10.2% with headache, which is similar to previous estimates of 2–16% reporting headache as an isolated initial symptom.[5,6] This is not surprising for two reasons. The first is the possibility of under-recording, as discussed above; the second is that the symptoms had to be deemed important enough for patients to have consulted their doctor. This is a much higher threshold than applied in previous studies where patients with a tumour were asked about their symptoms retrospectively. As the clinical problem of how and whom to select for further investigation is stationed in the consulting room (not in the population as a whole), it is appropriate to use data derived from the consulting room.

Implications for clinical practice and future research

Headache was strongly associated with primary brain tumours, yet the PPV was extremely small, at less than 1 in 1000. Even when there was a second symptom, such as confusion, the PPV only approached 3.9 in 1000. This is very reassuring, and provides support to doctors who may feel pressured

into referral.[19] In contrast, the risk from seizures was much higher, at 1.2% overall for new-onset seizures reported to primary care, rising to 2.3% if the patient was >60 years of age. This compares with tertiary care figures of 6–7%.[9–11] The difference probably reflects the population being studied, in that hospital attenders are a selected population, even with such a dramatic event as a first seizure.

The study used a robust definition of a first seizure: patients so labelled had no previous anticonvulsant therapy or seizure recorded. This may not have been the case for hospital-based studies. Another possibility is misdiagnosis of seizures, as approximately a quarter of epilepsy is misdiagnosed, particularly by generalists.[20,21] Assuming misdiagnosis occurred mainly in the control group, the PPVs in this study may be underestimated by a quarter. Nonetheless, 1.2% (or a quarter higher) is still an appreciable risk, and brings into question recent UK guidance about neuroimaging in epilepsy.[13] The recommendation that patients with idiopathic epilepsy need not have a brain scan is, to an extent, a circular argument, as it is difficult to label the epilepsy idiopathic without a negative scan. In practice, most neurologists perform a scan on all patients with new seizures. The results suggest that they are right to do so, even though a very high percentage will not show a tumour.

The other symptoms — confusion, weakness, motor loss, memory loss, and visual disorder — were each independently associated with brain tumours, but were individually of very low risk. All these features would prompt the generalist to do a neurological examination, including looking for papilloedema. Both motor loss and memory loss would generally lead to neuroimaging (scanning in motor loss looking primarily for a stroke; and in memory loss, seeking alternatives to Alzheimer's disease, such as hydrocephalus). The remaining three symptoms would rarely lead to imaging if they were isolated; results suggest that this is reasonable practice.

Overall, the results are reassuring. The incidence of primary brain tumours in primary care is very low. Several features are linked with tumours, but all of them are much more commonly caused by a different condition. The results suggest that neuroimaging is appropriate for all new-onset epilepsy, but is unnecessary in patients with isolated headache at presentation. Even with a dataset as large as the GPRD, it was impossible to identify specific second symptoms accompanying headache that would change this recommendation. This may require a prospective study of headache, but such a study will have to be extremely large to overcome the rarity of brain tumours.

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Ethics committee

Scientific and Ethical Advisory Group of the GPRD (reference number 784R)

Competing interests

David Kernick chairs the British Association for the Study of Headache. This body receives educational support from individual pharmaceutical companies. No company had any input of any nature into this study or paper

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REFERENCES

1. Giordana MT, Cordera S, Boghi A. Cerebral metastases as first symptom of cancer: a clinico-pathologic study. *J Neurooncol* 2000; **50(3):** 265–273.
2. Suwanwela N, Phanthumchinda K, Kaoropthum S. Headache in brain tumor: a cross-sectional study. *Headache* 1994; **34(7):** 435–438.
3. Snyder H, Robinson K, Shah D, *et al*. Signs and symptoms of patients with brain tumors presenting to the emergency department. *J Emerg Med* 1993; **11(3):** 253–258.
4. Jaeckle KA. Causes and management of headaches in cancer patients. *Oncology* 1993; **7(4):** 27–31.
5. Iversen H, Strange P, Sommer W, Tjalve E. Brain tumour headache related to tumour size, and location. *Cephalalgia* 1987; **6(Suppl 7):** 394–395.
6. Grant R. Overview: brain tumour diagnosis and management. Royal College of Physicians Guidelines. *J Neurol Neurosurg Psychiatry* 2004; **75(Suppl 2):** ii18–23.
7. Schwartzbaum J, Jonsson F, Ahlbom A, *et al*. Prior hospitalization for epilepsy, diabetes, and stroke and subsequent glioma and meningioma risk. *Cancer Epidemiol Biomarkers Prev* 2005; **14(3):** 643–650.
8. Lowry JK, Snyder JJ, Lowry PW. Brain tumors in the elderly: recent trends in a Minnesota cohort study. *Arch Neurol* 1998; **55(7):** 922–928.
9. Cockerell OC, Johnson AL, Sander JW, *et al*. Mortality from epilepsy: results from a prospective population-based study. *Lancet* 1994; **344(8927):** 918–921.
10. King MA, Newton MR, Jackson GD, *et al*. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. *Lancet* 1998; **352(9133):** 1007–1011.
11. Ramirez-Lassepas M, Morillo L, Gumnit R, Cipolle R. Value of computed tomographic scan in the evaluation of adult patients after their first seizure. *Ann Neurol* 1984; **15(6):** 536–543.
12. Vasconcelos D. Epileptic seizures as initial symptom of intracranial tumors. A prospective study in adults. *Gaceta Medica de Mexico* 1990; **126(3):** 169–174.
13. National Institute for Health and Clinical Excellence. *The diagnosis and care of children and adults with epilepsy.* Report no: CG20. NICE: London, 2004.
14. Kaba SE, Kyritsis AP. Recognition and management of gliomas. *Drugs* 1997; **53(22):** 235–244.
15. Salander P, Bergenheim AT, Hamberg K, Henriksson R. Pathways from symptoms to medical care: a descriptive study of symptom development and obstacles to early diagnosis in brain tumour patients. *Fam Pract* 1999; **16(2):** 143–148.
16. Knottnerus JA. *The evidence base of clinical diagnosis.* London: BMJ Books, 2002.
17. Cancer Research UK. *Incidence Statistics.* London: Cancer Research UK, 2003.
18. Boiardi A, Salmaggi A, Eoli M, *et al*. Headache in brain tumours: a symptom to reappraise critically. *Neurol Sci* 2004; **25(Suppl 3):** S143–S147.
19. Morgan M, Jenkins L, Ridsdale L. Patient pressure for referral for headache: a qualitative study of GPs' referral behaviour. *Br J Gen Pract* 2007; **57(534):** 29–35.
20. Scheepers B, Clough P, Pickles C. The misdiagnosis of epilepsy: findings of a population study. *Seizure* 1998; **7(5):** 403–406.
21. Smith D, Defalla B, Chadwick D. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. *QJM* 1999; **92(1):** 15–23.