

Review

Symptomatic diagnosis of cancer of the brain and central nervous system in primary care: a systematic review

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Abstract

Background. We performed a systematic review of diagnostic studies of symptomatic patients in primary care to quantify the risk of brain/central nervous system (CNS) cancer in patients presenting in primary care with symptoms that may indicate brain/CNS cancer.

Objective. To quantify the risk of brain/CNS cancer in symptomatic patients presenting in primary care.

Methods. We searched Medline, Premedline, Embase, the Cochrane Library, Web of Science and ISI Proceedings (1980 to August 2014) and PsychInfo (1980 to February 2013) for diagnostic studies of symptomatic adult patients in primary care. Study quality was assessed using QUADAS-II and data were extracted to calculate the positive predictive values (PPVs) of symptoms, singly or in combination, for brain/CNS cancer.

Results. Six studies with 159938 patients were included. The PPVs of single symptoms were very low with only 'new-onset seizure' being above 1% in patients aged 18 years and above, rising to 2.3% in patients aged 60–69 years. In patients aged 15–24 years, the PPVs for the individual symptoms were also very low, with the highest, also for seizure, being 0.024%, similar to that in children aged 0–14 years of 0.02%. For symptom combinations, none of the PPVs were above 0.39%.

Conclusions. All the symptoms of brain tumours are individually low risk, apart from new-onset epilepsy. This provides a real diagnostic problem, as brain tumours have all the expected features seen with cancer diagnostic delay, with high proportions presenting as an emergency and having had multiple primary care consultations before referral, and the prognosis is poor. Improving these metrics can only be done by liberalizing investigation, although the health economics of that strategy is undetermined.

Key words: Brain neoplasms, central nervous system neoplasms, diagnosis, primary health care, symptoms.

Introduction

Brain tumours account for ~2% of all new tumours in the UK, with ~4500 new diagnoses each year (1). The overall annual incidence is 7 per 100 000. Primary brain tumours represent ~60% of these and are usually gliomas. Meningiomas represent a further quarter: they are usually benign, though can produce considerable morbidity, depending on the precise location. Endocrine tumours, especially

arising in the pituitary, equate to ~11% of the total (2). Secondary brain tumours are approximately three times more common than primary ones (3); in most such patients, the primary cancer has already been diagnosed, though a small proportion first present with cerebral metastases (4). Malignancies of central nervous tissue outside the brain may also occur, though these are much rarer, and have received less research attention. The estimated cost of brain tumours in Europe in 2010 was €5.2 billion (5).

Several symptoms of primary brain tumours have been described, usually arising from increased intracranial pressure or damage to cerebral tissue. Up to 70% of patients have a headache during the course of their illness, particularly in the final stages of their disease (6). The incidence of headache at the time of diagnosis is between 23% and 56% (6–8). Epileptic seizures may also occur, especially in younger patients (9,10). Other reported symptoms of brain tumours include confusion, dysphasia, hemiplegia, hemianopia, motor weakness, personality change and memory loss (11).

Most patients with symptoms of brain tumours present to primary care, although patient with new-onset epilepsy may present directly to emergency departments. As most symptoms associated with brain tumours are also common in patients without tumours, the decision whether—or not—to investigate for a possible tumour is difficult. This difficulty is compounded by the main investigation being imaging, which is relatively expensive; furthermore, imaging may identify innocent lesions, the so-called ‘incidentalomas’. Imaging is generally performed as a specialist investigation, though schemes extending this to primary care clinicians have been implemented (12,13). We sought to quantify the risk of brain cancer in patients presenting in primary care with symptoms that may indicate brain/central nervous system (CNS) cancer, in a systematic review as part of a revision of UK cancer guidance (14).

Methods

Criteria for considering studies for this review

We included only studies that were performed on a series of unselected or randomly selected patients presenting to primary care with symptoms that might indicate brain/CNS cancer. The studies could be prospective or retrospective, but had to report follow-up data for the included patients indicating whether they had brain/CNS cancer or whether their symptom was of a benign origin. The follow-up data could be obtained from tests or medical records. Diagnostic case-control studies where cases were patients with brain/CNS cancer and controls were (matched) patients without brain/CNS cancer that reported the prevalence of the symptoms in both patient groups and the outcome of interest [positive predictive value (PPV); see also below] were also included. We did not include studies reporting only on high-risk patients or studies conducted in settings other than primary care, such as secondary or tertiary care, or studies reporting only on patients with brain/CNS cancer.

Search methods for identification of studies

We searched Medline, Premedline, Embase, the Cochrane Library, Web of Science (SCI and SSCI) and ISI Proceedings from 1980 to 12 August 2014 as well as PsychInfo (1980 to 20 February 2013) using the search strategy outlined in the online [Supplementary Material](#). The search was performed by one of the authors (SB) who also screened the initial search results, excluding all obviously irrelevant studies. A second author (MSH) then screened the titles and abstracts of the remaining records, excluding further irrelevant studies and examining the full text of all potentially relevant studies. The final lists of included and excluded studies were agreed in consensus between two of the authors (MSH and WH).

Data collection and analysis

Data extraction and quality assessment of the included studies was performed by one author (MSH). For each included study, the following characteristics were extracted: study design, inclusion/exclusion criteria, setting, patient characteristics (number, age, gender, country,

any other relevant characteristics reported such as relevant history or comorbidities), definition of symptom, method of verification of diagnosis and any other relevant details reported in the studies. The risk of different biases associated with the included studies was assessed using the QUADAS-II tool for each of the included studies (15). For each reported symptom, we extracted the PPV or, where this was not reported, the number of patients with the symptoms who had brain/CNS cancer [true positives (TP)] and the number of patients with the symptoms who did not have brain/CNS cancer [false positives (FP)]. From these data, we calculated PPVs that formed the basis of the risk estimate using the conventional formula of $TP/TP + FP$. If three or more studies reported a given symptom, we aimed to meta-analyse the results to provide a summary estimate indicating the risk of brain/CNS cancer associated with each symptom. However, meta-analysis was not feasible due to the low number of studies reporting on individual symptoms and the variation in their study design.

Results

Results of the search

The search of all the databases identified 7555 (before de-duplication) possibly relevant papers of which 7525 papers were excluded based on title/abstract: 30 papers were obtained for full text review. Six of these 30 papers were included in this review (16–21), while 24 papers were excluded for the following reasons: follow-up period not deemed sufficient ($N = 2$) (22,23); narrative review ($N = 6$); no or insufficient verification of final diagnosis ($N = 4$); not patients presenting to primary care ($N = 3$); setting not primary care ($N = 1$); PPVs not reported or calculable ($N = 3$); case report ($N = 3$) and did not include any new data ($N = 2$).

Characteristics and methodological quality of included studies

[Table 1](#) provides a summary of the characteristics of the included studies and the online [Supplementary Materials](#) provide a detailed description and assessment of each study. The studies included a total of 159 938 patients with all 6 conducted in the UK. The reference standards employed in the studies were all follow-up. The studies reported on a number of single symptoms and symptom combinations, in children (17,19,21), teenagers and young adults (18) or adult (16,20) populations.

[Table 2](#) summarizes the risk-of-bias and applicability assessments for each of the included studies. The main bias and applicability concerns relating to patient selection were that this was not clearly consecutive or random in four of the studies (17–20), with one of the studies including non-malignant brain tumours (20).

Findings

Single symptoms

[Tables 3–5](#) list the PPVs for single symptoms in adult, teenage and young adult, and child patients. The PPVs of single symptoms were generally very low with only ‘new-onset seizure’ being above 1% in patients aged 18 years and above, rising to 2.3% in patients aged 60–69 years. [Table 4](#) also shows that in patients aged 15–24 years the PPVs for the individual symptoms were very low, with the highest, also for seizure, being 0.024%, similar to that for children aged 0–14 years of 0.02%.

Symptom pairs

In addition to single symptoms, two of the studies also reported information on PPVs for symptom combinations: Hamilton and Kernick (20) found that headache in combination with any other of

Table 1. Characteristics of the included studies on patients presenting to primary care with symptoms that might indicate brain/CNS cancer including method of verification of malignant/benign diagnosis

Study	Country	Design	Total number eligible	Number of patients with brain/CNS cancer	Reference standard
Ansell <i>et al.</i> (2010) (17)	UK	National population-based case-control study of children aged 1–14 years	480	195 (mean age of patients = 7.31 years; SE = 0.27 years)	Diagnosis of brain tumour in their primary care record
Dommett <i>et al.</i> (2013) (18,19)	UK	Population-based nested case-control study using data from the GPRD from children and young adults aged 0–24 years	5634	424 (0–4 years: N = 73; 5–14 years: N = 197; 15–24 years: N = 154)	Diagnosis of brain/CNS cancer in the GPRD
Hamilton and Kernick (2007) (20)	UK	Population-based nested case-control study using data from the GPRD from adults aged ≥18 years	19 570	2397 (of a total of 3505 cases with brain tumours, the remainder were benign; 584/2397 malignant tumours occurred in patients aged 60–69 years)	Diagnosis of brain tumour in the GPRD
Kernick <i>et al.</i> (2008) (16)	UK	Retrospective, consecutive patients using data from the GPRD from adults aged ≥18 years	85 679	107 (<50 years: N = 37; ≥50 years: N = 70)	1-year follow-up
Kernick <i>et al.</i> (2009) (21)	UK	Retrospective, consecutive patients using data from the GPRD from children aged 5–17 years	48 575	13	1-year follow-up

GPRD, UK General Practice Research Database (now renamed the Clinical Practice Research Datalink); SE, standard error.

Table 2. Risk-of-bias assessment for the included trials

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ansell <i>et al.</i> (2010) (17)	–	+	+	+	+	+	+
Dommett <i>et al.</i> (2013) (18,19)	–	+	+	+	+	+	+
Hamilton and Kernick (2007) (20)	–	+	+	+	?	+	+
Kernick <i>et al.</i> (2008) (16)	+	+	+	+	+	+	+
Kernick <i>et al.</i> (2009) (21)	+	+	+	+	+	+	+

‘+’ denotes low risk of bias/concerns about applicability; ‘?’ denotes unclear risk of bias/concerns about applicability; ‘–’ denotes high risk of bias/concerns about applicability.

the symptoms examined in their study was associated with a PPV of 0.39% [95% confidence interval (CI): 0.31–0.48] in patients aged 18 years or above. In children aged 0–14 years, Ansell *et al.* (17) reported that vomiting in combination with unsteadiness or visual difficulties had PPVs of 0.15% (95% CI: 0.01–0.1) and 0.088% (95% CI: 0.005–0.6), respectively, and that the PPV of headache in combination with unsteadiness was 0.085% (95% CI: 0.005–0.6). All other symptom combinations examined by Ansell *et al.* (17) had even lower PPVs.

Conclusions

To our knowledge, this is the first systematic review of the clinical features of brain/CNS cancer in primary care. Many of the features reported from secondary care studies were also relevant in primary care, though the likelihood of cancer with particular features was generally lower in primary care, reflecting the lower incidence of cancer in that population compared to specialist practice. In adults and teenagers, seizures were the symptom with the highest risk, but these risks were still small, with a highest estimate in adults of 2.3% in patients aged 60–69, and they were very small in other age groups,

being below 1 in 1000 for children, teenagers or young adults. More common features, such as headache, all represented much lower risks of brain/CNS cancer.

Strengths and weaknesses of the review

This review followed best practice methods (24). In particular, the setting for the inclusion of studies was primary care. This was crucial for the clinical question to be answered—which patients presenting to primary care may have a brain/CNS cancer, and so may benefit from imaging? Reviews including patients in the referred population generally find stronger associations between symptoms and disease, and are much less helpful in informing investigation or referral decisions.

As with any review, the findings depend upon the quality of the original studies. The more recent ones using electronic research databases were high quality, and of large size, despite the relative rarity of brain/CNS cancer. Several used case-control methods, which can lead to bias from patient selection. In this case, however, all patients present in the GPRD were used, reducing this concern. Two small studies conducted in US-based emergency departments were excluded due to insufficient follow-up periods

Table 3. PPVs for brain/CNS cancer for single symptoms in adult patients in descending order of frequency among the patients with brain/CNS cancer

Study	Symptom(s)	Patient group, age in years	Frequency of symptom in patients with brain/CNS cancer	PPV% (95% CI)
Hamilton and Kernick (2007) (20)	Headache	Patients ≥ 18 (N = 623)	362/3505 = 10%	0.09 (0.08–0.1)
Kernick <i>et al.</i> (2008) (16)	Undifferentiated headache	Patients 60–69 (N = 54)	54/767 = 7.0% ^a	0.12 (0.09–1.7) ^a
		Patients ≥ 18 (N = 63 921)	Not applicable, but PPV based on 97/63 921 ^b	0.15 (0.12–0.19)
Kernick <i>et al.</i> (2008) (16)	Primary headache	Patients < 50 (N = 40 866)	Not applicable, but PPV based on 32/40 866 ^b	0.08 (0.05–0.11)
		Patients ≥ 50 (N = 23 055)	PPV based on 65/23 055 ^b	0.28 (0.22–0.36)
		Patients ≥ 18 (N = 21 758)	PPV based on 10/21 758 ^b	0.045 (0.023–0.088)
		Patients < 50 (N = 16 282)	PPV based on 5/16 282 ^b	0.03 (0.01–0.08)
Hamilton and Kernick (2007) (20)	Motor loss	Patients ≥ 18 (N = 5476)	PPV based on 5/5476 ^b	0.09 (0.03–0.23)
Hamilton and Kernick (2007) (20)	New-onset seizure	Patients ≥ 18 (N = 1039)	308/3505 = 8.8%	0.026 (0.024–0.03)
Hamilton and Kernick (2007) (20)	Confusion	Patients ≥ 18 (N = 162)	154/3505 = 4.4%	1.2 (1–1.4)
		Patients 60–69 (N = 35)	35/808 = 4.3% ^a	2.3 (1.6–3.3) ^a
Hamilton and Kernick (2007) (20)	Weakness	Patients ≥ 18 (N = 156)	109/3505 = 3.1%	0.2 (0.16–0.24)
Hamilton and Kernick (2007) (20)	Memory loss	Patients ≥ 18 (N = 137)	95/3505 = 2.7%	0.14 (0.11–0.18)
Hamilton and Kernick (2007) (20)	Visual disorder	Patients ≥ 18 (N = 101)	37/3505 = 1.1%	0.036 (0.026–0.052)
Hamilton and Kernick (2007) (20)		Patients ≥ 18 (N = 97)	35/3505 = 1%	0.035 (0.025–0.051)

^aNot reported in the paper but information available from authors.

^bStrictly, the PPV is not applicable, but it has been estimated from the numbers given.

Table 4. PPVs for brain/CNS cancer for single symptoms in teenage–young adult patients in descending order of frequency among the patients with brain/CNS cancer

Study	Symptom(s)	Patient group, age in years	Frequency of symptom in patients with brain/CNS cancer	PPV% (95% CI)
Dommett <i>et al.</i> (2013) (18)	Headache	All included cases and controls aged 15–24	33/154 = 21.4%	0.015 (0.0077–0.0276)
	Seizure		18/154 = 11.7%	0.024 (0.0082–0.0695)
	Visual symptoms		13/154 = 8.4%	0.07 ^a
	Vomiting		11/154 = 7.1%	0.012 (0.0041–0.031)
	Pain		11/154 = 7.1%	0.0029 (0.0014–0.006)
	≥3 consultations		73/154 = 47.4%	0.0023 (0.0019–0.0029)

^aThe authors did not report a PPV as no controls had this feature. For this review, one control had been re-assigned to having visual symptoms, allowing a broad estimation of the PPV.

(1–4 weeks and 1–7 months, respectively) (22,23). Emergency departments are generally considered to be primary care, though the spectrum of disease seen in them differs from usual general or family practice. It was debatable whether these two studies should have been included in this review. However, as no cancers were found in either study, their results are relatively uninformative, except to demonstrate that both weakness and dizziness appear to be very low risk symptoms.

Implications of the findings for clinical practice

The commonest symptom of brain tumours in primary care is headache. This was recorded in the primary care records of 10% of adults in the year before diagnosis of a brain tumour, and of over 20% of children and teenagers and young adults. It is probable that these represent under-estimates, as not every symptom is recorded in medical records, and some are recorded in a part of the notes that is not accessible routinely by researchers (25). This under-recording is likely to have affected controls as well, so the PPVs (which are based on the ratio between symptom frequency in cases and symptom frequency in controls) are likely to be reasonably accurate. In all age groups, PPVs for headache were very low – and lower still if

the doctor was able to make a diagnosis of primary headache (21). Even when the headache was accompanied by a second symptom, the risks of a brain tumour remained below 1% for both adults and children (17,20). This should help support clinicians discuss the merits and demerits of possible imaging, particularly when a patient with a headache specifically requests it.

In contrast, new-onset epileptic seizures were both less common than headache and of higher risk. Fewer than 5% of adults with a brain tumour had a preceding seizure—and under-recording of this symptom is much less likely than under-recording of headache (20). Young children had a similar low prevalence of seizures (19), whereas teenagers and young adults had the highest, at 11.7% (18). These figures for prevalence of epilepsy with brain tumours are similar to a population study using routine Swedish pathology data (10). As epileptic seizures are common in patients without brain tumours, PPVs were relatively low, with the highest value being 2.3% in the 60–69 age group. Current UK guidance for a new-onset seizures suggests MRI imaging, except where idiopathic generalized or benign focal epilepsy have been diagnosed (26). Such imaging will identify a brain tumour, as well as other rarer structural causes of epilepsy.

Table 5. PPVs for brain/CNS cancer for single symptoms in children in descending order of frequency among the patients with brain/CNS cancer

Study	Symptom(s)	Patient group, age in years	Frequency of symptom in patients with brain/CNS cancer	PPV % (95% CI)
Dommett <i>et al.</i> (2013) (19)	Headache 0–3 months before diagnosis	All CNS cancer patients and controls aged 0–14	58/270 = 21.5%	0.03 (0.02–0.06)
Kernick <i>et al.</i> (2009) (21)	Headache (any type)	All included patients aged 5–17	PPV based on 13/48 575 ^a	0.03 (0.01–0.05)
Kernick <i>et al.</i> (2009) (21)	Primary headache		PPV based on 0/9321 ^a	0 (0–0.05)
Kernick <i>et al.</i> (2009) (21)	Undifferentiated headache		PPV based on 13/38 705 ^a	0.03 (0.02–0.06)
Dommett <i>et al.</i> (2013) (19)	Vomiting 0–3 months before diagnosis	All CNS cancer patients and controls aged 0–14	55/270 = 20.4%	0.04 (0.02–0.07)
Dommett <i>et al.</i> (2013) (19)	Abnormal movement 0–3 months before diagnosis		32/270 = 11.9%	0.11 (0.03–0.35)
Dommett <i>et al.</i> (2013) (19)	Visual symptoms 0–3 months before diagnosis		21/270 = 7.8%	0.07 (0.02–0.24)
Dommett <i>et al.</i> (2013) (19)	Pain 0–3 months before diagnosis		14/270 = 5.2%	0.03 (0.01–0.08)
Dommett <i>et al.</i> (2013) (19)	Seizure 0–3 months before diagnosis		10/270 = 3.7%	0.02 (0.01–0.06)
Dommett <i>et al.</i> (2013) (19)	≥3 consultations		137/270 = 50.7%	0.01 (0–0.01)

^aStrictly, the PPV is not applicable but it has been estimated from the numbers given.

Brain tumours may also present with a progressive loss of neurological function, which may have a motor component, a sensory component or loss of higher cerebral functions, such as memory. Structural imaging is recommended in suspected dementia, in part to identify other pathologies, as well as differentiation into dementia subtypes (27). This review identified very low PPVs for brain tumours with motor symptoms, memory loss or visual disorders—in all age groups. Even so, it can be argued that imaging is of value, not just for identification of possible malignancy, but for other possible benign conditions causing the symptoms. Historically in the UK, cerebral imaging has been the province of specialists, though schemes of primary care access to scanning have been established. The yield of treatable lesions has been low, commensurate with the findings of this review (13,28). The health economics of primary care imaging compared to specialist imaging have not been reported, but the former is likely to be cheaper.

Two aspects of this review suggest possible future research topics. Although the PPVs of headache plus a second symptom were low, it remains possible some headache combinations are truly high risk. This is important because headache is the most prevalent symptom in brain tumours, yet the PPVs do not support investigation for headache *per se*. Secondly, the benefits of expediting brain tumour diagnosis are largely unknown. Even if mortality gains from expedited diagnosis are small (and this is not certain), morbidity benefits may be considerable.

This review demonstrated that all symptoms of brain tumours are individually low risk, with the exception of new-onset epilepsy. This provides a real diagnostic problem, as brain tumours have all the expected features seen with cancer diagnostic delay. A high proportion present as an emergency (29); a high proportion has multiple primary care consultations before referral (30) and the prognosis is poor. Improving these metrics can only be done by liberalizing investigation, though as yet there is not the health-economic evidence to support doing so.

Supplementary material

Supplementary material is available at *Family Practice* online.

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