Diagnosing adult primary brain tumours: can we do better?

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In late 2015-early 2016, a public e-petition prompted a House of Commons Select Committee enquiry and subsequent parliamentary debate into brain tumour research, highlighting the devastating impact that brain tumours have on patients and their families. Two key areas of concern were the potential impact of diagnostic delays on survival and quality of life for patients and their families, and the low priority given to brain tumour research by government and funders.[1]

The prognosis for primary brain tumours remains poor; only 40% of people diagnosed with malignant brain tumours live for more than a year, and less than 20% for more than five years.[2] Although patients with brain/CNS tumours lose more than 20 years of life on average, the highest among commoner cancer types,[2] improving early diagnosis of brain tumours has long been perceived as unfeasible due to poor symptom specificity. However, during the last decade the median total diagnostic interval for paediatric brain tumours has halved (101 days in 2006 to 47 days in 2013), probably due to a range of factors including the publication of NICE guideline CG27 on referral for suspected cancer in June 2005, the two-week urgent referral pathway, and the UK-wide HeadSmart public and professional awareness campaign, focusing on the symptoms and signs of brain tumours in children and young people.[3,4] Learning from this success, can we now improve time to diagnosis for adult primary brain tumours?

CURRENT EXPERIENCE OF ADULTS DIAGNOSED WITH PRIMARY BRAIN TUMOURS

Multiple primary care consultations occur commonly among adults subsequently diagnosed with primary brain tumours. Evaluation of the National Cancer Patient Experience Surveys

showed that 39% of brain/CNS cancer patients had three or more pre-referral consultations with a GP compared to an average of 25% for all cancers; furthermore, a third reported declining health while waiting to see a hospital doctor compared with a fifth of patients across all tumour groups.[5] National primary care audit data analyses reported similar findings, and also demonstrated longer diagnostic intervals related to multiple primary care consultations: a quarter of brain cancer patients with three to four, and five or more consultations experienced intervals longer than 62 and 166 days respectively.[6]

Emergency presentations are a common route for diagnosis of adult brain tumours, with 61% presenting through this route between 2006 and 2013. This figure was second only to acute lymphoblastic leukaemia. This matters, as emergency presentations are associated with a significantly lower one-year relative survival compared to other non-emergency routes to diagnosis,[7] and emergency brain surgery is associated with an increased risk of morbidity and mortality. Advanced disease also comes with a greater risk of acquired neurological disability due to tumour-related brain injury.

BARRIERS TO DIAGNOSING ADULT PRIMARY BRAIN TUMOURS

The 2015 NICE guidelines for recognition and referral of suspected cancer lowered the threshold for GPs to refer suspected adult brain and CNS cancers for urgent investigation (CG12), and some areas also now have direct access brain MRI available. In spite of these developments, diagnosing brain tumours is challenging for GPs, as the vast majority of patients with neurological symptoms are diagnosed with benign disease and the probability of having a patient with a brain tumour is very low. The positive predictive values (PPVs) of either single symptoms (such as headaches, weakness, confusion, memory loss, and visual or motor disturbance) or symptom combinations for brain/CNS cancer are all low (less than 1%), with the exception of new-onset or first seizure (although it is worth noting that current NICE guidance for investigation of a first seizure (CG137) does not routinely recommend early imaging, thus potentially delaying diagnosis of tumours presenting through this route).[8] Currently, we understand little about why patients present as emergencies or make several visits to the GP before referral, and the presentation, assessment and diagnosis of brain tumours is not well described. Evidence is lacking about how adult patients with primary brain tumours detect and assess their symptoms, decide to seek help, and their experiences of pathways to diagnosis. For other cancer sites a number of sociodemographic factors (such as age, gender, living alone, educational level, health literacy), clinical factors (such as presenting symptom/s and co-morbidities), and health-related behaviours (such as self-medication), have been associated with time from first symptom detection to diagnosis (known as the total diagnostic interval). It is likely that these factors also affect presentation with a brain tumour. Among the few qualitative studies undertaken worldwide which explore the pathway to diagnosis for brain tumour patients, one set in Sweden and one in the UK have both shown that subtle or non-specific

symptoms or a personality change due to the developing tumour, may delay help-seeking. Furthermore, patients may be unaware of, or lack insight into, some symptoms (although these may be observed by family members, friends or work colleagues), and thus do not report them.[9,10]

HOW CAN WE EXPEDITE DIAGNOSIS OF ADULT PRIMARY BRAIN TUMOURS?

There is an urgent need for rigorous multi-methods research in order to better understand what may impede and facilitate the diagnosis of primary brain tumours. A robust theoretical framework, with a focus on understanding factors affecting patients' symptom appraisal and help-seeking behaviour, has been successfully applied to other cancers (including colorectal cancer and melanoma),[11] and could similarly illuminate patient pathways to presentation and diagnosis with brain tumours in order to inform awareness campaigns. Once patients present to primary care, GPs need risk assessment tools to triage and direct appropriate management including rapid access to CT scans and to neurological services. Diagnostic capacity will need to be increased to meet demand, and alternative models of assessment could draw on those being developed for childhood cancer. Biomarkers are likely to provide the most effective means to expediting diagnosis but there is currently a dearth of candidates. Pharmacists and opticians may also be the patient's first point of contact with healthcare, and need close involvement in revised care pathways. Given the high proportion of brain tumours that are diagnosed as an emergency, there is a particular need to better understand the mechanisms leading to emergency diagnosis. For example, we need to distinguish between emergency diagnosis at first presentation versus emergency diagnosis in patients who have sought help previously, and the underlying reasons for these scenarios, including whether emergency presentation was potentially avoidable.

Could more timely diagnosis improve survival and quality of life? The James Lind Alliance Priority Setting Partnership (JLA PSP) in Neuro-Oncology has identified this among their 'Top 10' priorities for future research.[12] In a recent Delphi study on the effects of expedited cancer diagnosis, clinical expert participants judged that brain tumour patients would experience benefits in morbidity, including provision of symptom relief and possible improvement in psychological wellbeing, despite less mortality benefit compared to other cancers.[13] Survival rates differ markedly for different tumour types and grades, and a key challenge associated with determining the impact of early diagnosis is tumour heterogeneity and resulting low patient numbers for each individual tumour type.

Nevertheless, research that illuminates the barriers and facilitators to early diagnosis could help reduce time to diagnosis for adult primary brain tumours, and potentially alleviate the devastating impact on patients and their families. This could be achieved through informing a campaign along the lines of HeadSmart, focused on adults, and combining high quality,

evidence-based guidance for primary care clinicians with public awareness-raising regarding the range of symptoms that might be suspicious of a brain tumour.

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