Presentation of childhood CNS tumours: a systematic review and meta-analysis

Sophie Wilne, Jacqueline Collier, Colin Kennedy, Karin Koller, Richard Grundy, David Walker

Summary

Background Suspicion of a CNS tumour is classically raised by symptoms of raised intracranial pressure, focal deficits (including seizures), or papilloedema. Development of guidelines is needed for the identification and referral of children who might have a CNS tumour. We did a systematic literature review and meta-analysis to identify the clinical presentation of childhood CNS tumours to provide evidence to support the development of guidelines to assist with the identification and referral for imaging of children who might have a central nervous system tumour.

Methods Medline, Embase, and PubMed were searched for cohort studies and case series in children, published between January, 1991, and August, 2005, detailing the symptoms and signs at diagnosis of a CNS tumour.

Findings 74 papers (n=4171) met the inclusion criteria. 56 symptoms and signs at diagnosis were identified, ranked by frequency, and clustered according to age, anatomical criteria, and genetic criteria. The most frequent symptoms and signs at diagnosis were: headache (33%), nausea and vomiting (32%), abnormalities of gait and coordination (27%), and papilloedema (13%) for intracranial tumours; macrocephaly (41%), nausea and vomiting (30%), irritability (24%), and lethargy (21%) for children aged under 4 years with intracranial tumours; reduced visual acuity (41%), exophthalmia (16%), and optic atrophy (15%) for children with an intracranial tumour and neurofibromatosis; nausea and vomiting (75%), headache (67%), abnormal gait and coordination (60%), and papilloedema (34%) for posterior fossa tumours; unspecified symptoms and signs of raised intracranial pressure (47%), seizures (38%), and papilloedema (21%) for supratentorial tumours; headache (49%), abnormal eye movements (21%), squint (21%), and nausea and vomiting (19%) for central brain tumours; abnormal gait and coordination (78%), cranial nerve palsies (52%), pyramidal signs (33%), headache (23%), and squint (19%) for brainstem tumours; and back pain (67%), abnormalities of gait and coordination (42%), spinal deformity (39%), focal weakness (21%), and sphincter disturbance (20%) for spinal-cord tumours. Other features noted were weight loss, growth failure, and precocious puberty. Symptoms of raised intracranial pressure were absent in more than half of children with brain tumours. Other neurological features were heterogeneous and related to tumour location.

Interpretation Apart from raised intracranial pressure, motor and visual system abnormalities, weight loss, macrocephaly, growth failure, and precocious puberty also suggest presence of an intracranial tumour. Children with signs and symptoms that could result from a CNS tumour need a thorough visual and motor system examination and an assessment of growth and pubertal status. Occurrence of multiple symptoms and signs should alert clinicians to possible CNS tumours.

Lancet Oncol 2007; 8: 685–95

Published Online
July 18, 2007
DOI:10.1016/S1470-2045(07)70207-3

See Reflection and Reaction page 664

Children's Brain Tumour Research Centre, Academic Division of Child Health (S Wilne MBBS, K Koller PhD, Prof R Grundy MBChB, Prof D Walker MBBS), **and School of Nursing, Faculty of Medicine & Health Sciences** (Prof J Collier PhD), **University of Nottingham, Queen's Medical Centre, Nottingham; and Department of Child Health, University of Southampton, Southampton General Hospital, Southampton, UK** (Prof C Kennedy MBBS)

Correspondence to:
Dr Sophie Wilne, Children's Brain Tumour Research Centre, Academic Division of Child Health, University of Nottingham, Queens Medical Centre, Nottingham NG7 2UH, UK
sophie.wilne@nottingham.ac.uk

Introduction

Life-threatening clinical conditions in childhood are seen infrequently in developed countries.[1,2] Screening of the few serious diagnoses from the many self-limiting conditions and fluctuations in developmental processes and behaviour is a major diagnostic challenge in primary and secondary health care.[3,4] Cancer affects one in 600 children under 16 years and thus represents a moderate health risk similar to cerebral palsy, diabetes mellitus, and meningitis.[5–7] A quarter of childhood cancers arise in the CNS and account for the largest number of cancer deaths in childhood.[1] 60% of survivors are left with pronounced disability.[8–12] CNS tumours are therefore common in the context of life-threatening childhood disease. All health-care professionals seeing children should be able to identify symptoms and signs that could result from a CNS tumour and refer or investigate appropriately.

Despite advances in neuroimaging, the timely diagnosis of CNS tumours in the UK remains difficult.[13] The varied presentation and perceived rarity (resulting in a low priority in the differential diagnosis) of CNS tumours in childhood underlie this problem. Many of the initial symptoms and signs of CNS tumours also occur with other more common and less serious childhood disorders such as gastroenteritis, migraine, and behavioural problems. Conventional teaching is that CNS tumours present with symptoms of raised intracranial pressure (early morning headache with vomiting and papilloedema) with or without focal neurological signs.[14,15] Research in the pre-CT era has identified comprehensive lists of symptom and sign clusters with which neurologists and other paediatric specialists are highly familiar. Currently, expanded access to neuroimaging and the pressure to accelerate cancer diagnoses is placing a much broader group of doctors in the position to initiate imaging either directly or through an urgent cancer referral. A period of diagnostic uncertainty often precedes the diagnosis of a

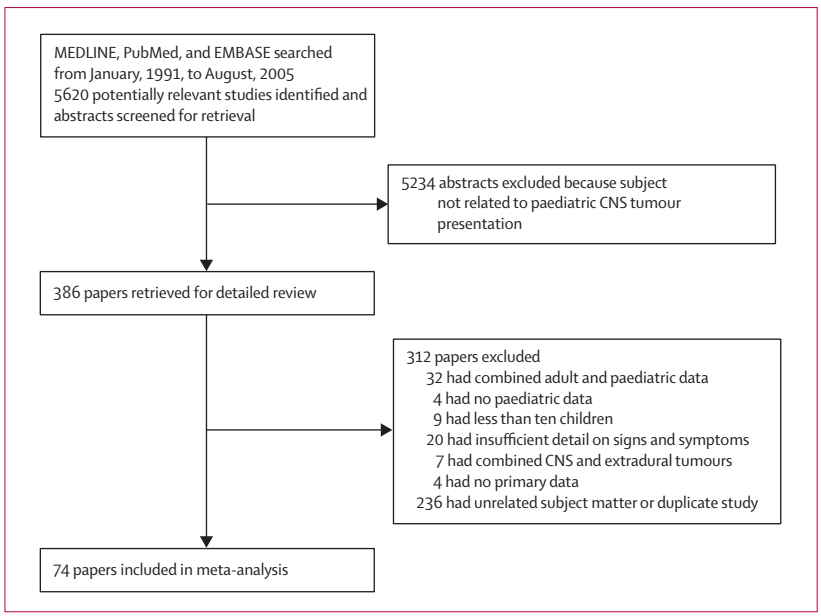

Figure 1: **Progress through the meta-analysis**

CNS tumour, which patients and their families find extremely distressing, and any perception that the medical response has been inadequate, incompetent, or delayed may be associated with legal dispute.[16]

In 1991, the Childhood Brain Tumour Consortium[17] reported the symptoms and signs at diagnosis for 3291 children diagnosed with a brain tumour in 1930–79. To provide a more contemporary cohort, we undertook a systematic review and meta-analysis of the presenting symptoms and signs in paediatric CNS tumours detailed in subsequent publications. The literature review was done as the initial stage in a project devising guidance to help health-care professionals identify children who might have a CNS tumour and who thus need fast-track imaging.

Methods

Identification of studies and inclusion criteria

We searched MEDLINE, PubMed, and EMBASE without language restriction, from January, 1991, to August, 2005. Key words were: "brain tumour(s), "brain tumor(s)", "brain neoplasm(s)", "spinal cord tumour(s)", "spinal cord tumor(s)", "spinal cord neoplasm"; and "diagnosis"; and "sign(s)" or "symptom(s)". Retrieved references were restricted to "all child". Abstracts were screened by a researcher (SW); those unrelated to CNS tumours or discussing an area unrelated to clinical presentation were excluded. Papers with abstracts discussing tumour presentation, tumour diagnosis, or clinical symptoms and signs were retrieved for detailed review.

We included all case-series or cohort studies describing symptoms and signs at diagnosis for a minimum of ten children diagnosed with a CNS tumour and published after February, 1991. Non-English language papers were translated.

Data collection

Numbers of children in every study with a symptom or sign at diagnosis were recorded on a standard data extraction form. Information on symptoms and signs varied between studies. Some studies had very detailed records on individual symptoms and signs (eg, headache, vomiting, papilloedema), whereas others reported symptoms in clusters or complexes (eg, symptoms of raised intracranial pressure). Symptoms and signs were recorded as described in the individual studies. If a symptom or sign was not recorded in a study, we assumed it not to occur in that population.

Statistical analysis

Analysis was done with meta-disc version β 1.1.1. We combined proportions (%) of children with each symptom or sign at diagnosis using one-variable relationship meta-analysis. The effect size for each symptom and sign was calculated in the individual studies and weighted according to its variance, and these effect sizes were then summed (for each symptom and sign) and the total effect size was then divided by the sum of the weights to give a mean effect size (pooled proportion).[18]

In meta-disc, proportions (as well as likelihood ratios and diagnostic ratios) could be pooled with either the Mantel-Haenszel method (fixed-effects model) or, to incorporate variation between studies, with the DerSimonian Laird method (random-effects model). In the present study, heterogeneity was indicated beyond what could be expected by chance alone, by significant Q statistics and high inconsistency (I^2) statistics. The DerSimonian Laird method was selected because variability was expected across the papers, and a random-effects model was used.[18] Symptoms and signs occurring in 5% or more of the meta-analysis population were reported. Two papers[19,20] reported optic atrophy and papilloedema and one paper[21] lethargy and irritability as a combined category. Since these papers reported detailed information for other symptoms and signs, they were included in the meta-analysis but excluded from the analysis of the combined symptoms or signs. In one report,[19] visual acuity was not assessed in the complete cohort and, therefore, was excluded from the meta-analysis of visual acuity.

The following subgroup analyses were undertaken: all intracranial tumours; intracranial tumours in children aged under 4 years; children with an intracranial tumour and neurofibromatosis; posterior fossa tumours; supratentorial (excluding central) tumours; central tumours (third ventricle, tectum, pineal gland, pituitary gland, thalamus, hypothalamus, optic pathway, and basal ganglia); brainstem tumours; and spinal-cord tumours.

Analysis of all intracranial tumours was undertaken to provide a summary of paediatric intracranial tumour presentation. Children aged under 4 years usually cannot clearly describe symptoms such as headache, nausea, and diplopia, and therefore have a different presentation to