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Identifying brain tumours in children and young adults

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Healthcare professionals caring for children need to promptly identify the child or young person with a serious underlying condition from the majority who present with minor self limiting illness. Recognising when a child might have cancer can be particularly difficult. Despite the perception that cancer is rare in children, an average general practice will see a child or young person with a new cancer every six years, and a quarter of the tumours will be brain tumours (personal communication, Patricia O'Hare, 2013).[1] Early diagnosis can be crucial—evidence from cohort studies shows that it can improve short term and long term outcomes.[2-5] This review summarises current evidence on the presentation and recognition of brain tumours in children and young adults and provides an overview of the treatment and long term care strategies for this population.

What brain tumours occur in children?

The term "brain tumour" encompasses a large number of different tumour types that have different cells of origin and clinical course (table 1). The most common brain tumours in children and young people are pilocytic astrocytomas, medulloblastomas, ependymomas, high grade gliomas, and germ cell tumours.[6 7] Histologically, brain tumours are assigned a World Health Organization grade of 1-4 according to features suggesting malignancy, such as pleomorphic nuclei, high mitotic rate, and vascular invasion. Grades 1 and 2 are regarded as benign and 3 and 4 as malignant,[8] although the correlation between histological grade and patient outcome is poor. A low grade tumour that is not susceptible to treatment and is in a crucial area of the brain, such as the brain stem, is more likely to be fatal than certain high grade tumours that are resectable and sensitive to chemoradiotherapy.[9 10]

What are the risk factors for brain tumours in children?

As is true for most childhood cancers, no cause or trigger can be identified for most brain tumours. Several genetic syndromes, however, are associated with an increased risk of brain tumours (table 2 on bmj.com)[7]

The development of some childhood brain tumours is related to changes in the local tumour (brain) environment that are linked to age. Children with neurofibromatosis type 1 have a 10-20% risk of developing an intracranial pilocytic astrocytoma, particularly in the optic pathways, owing to loss of neurofibromin 1 (the product of the *NF1* gene), which is a negative regulator of cell growth through the mitogen activated protein kinases/extracellular signal regulated kinases pathway. Not every child with neurofibromatosis type 1 develops an optic pathway glioma, and almost all children with the condition who develop one are under the age of 7 years. Therefore there is an interaction between germline *NF1* mutations, the age of the child, and another unknown factor that results in the development of an optic pathway glioma in some but not all children with the condition.

Studies in mouse models of neurofibromatosis type 1 have shown that reduced cAMP production in the brain is needed for the development of tumours. Mouse and human tissue studies have shown that cAMP levels vary with polymorphisms in cAMP regulators,[11] and that cAMP levels in the optic pathway are lower in young children than in older ones. These findings explain why optic pathway gliomas occur in only some young children with neurofibromatosis type 1.

Intracranial germ cell tumours provide another less well understood example. With the exception of mature teratomas, intracranial germ cell tumours are very rare in young children but are much more common as adolescence proceeds. Presumably, this is a result of the hormonal drive to gonadal development interacting with potential tumour cells within the brain.

Case-control and cohort studies have shown that exposure to ionising radiation is the only environmental factor associated with brain tumours.[7] Brain or central nervous system radiotherapy for a previous cancer is the most common cause of exposure to high doses of ionising radiation, and secondary high grade gliomas and meningiomas have been reported in these populations.[12] Children who undergo computed tomography (CT) also have a risk of radiation induced cancer. A recently published epidemiological study found 608 excess cancers (of which 147 were brain tumours) in 680 211 patients who had a CT scan between the ages of 0 and 19 years, with children less than 5 years being particularly at risk.[13]

How do brain tumours present in children and young people?

The symptoms and signs of brain tumours are varied and determined by the part of the brain affected, the developmental stage and ability of the child or young person, and whether or not intracranial pressure is raised. There is usually a clinical evolution in the time period between initial

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- Managing cows' milk allergy in children (*BMJ* 2013;347:f5424)
- Personality disorder (*BMJ* 2013;347:f5276)
- Dyspepsia (*BMJ* 2013;347:f5059)

SUMMARY POINTS

- Each week in the United Kingdom, 10 children and young people are diagnosed with a brain tumour
- An average general practice sees a new childhood cancer every six years; a quarter of these will be brain tumours
- Earlier diagnosis of brain tumours in children and young adults improves long term outcomes
- Diagnosis requires recognition of the specific combinations of symptoms and signs seen with tumours in different areas of the brain and with raised intracranial pressure, followed by brain imaging
- The developmental stage of the child affects tumour presentation; young children may not be able to describe visual abnormalities and headache
- Include a focused history (looking for corroborative symptoms and risk factors) and assessment of vision, motor skills, growth, and puberty in children or young people who present with symptoms or signs suggestive of a brain tumour

Table 1 | Classification of brain tumours that occur in children and young people

Tumour group	Tumour	Location	WHO* grade	Approximate frequency (%)
Embryonal tumours: arise from transformation of undifferentiated and immature neuroepithelial cells	Medulloblastoma	Cerebellum	4	20
	Central primitive neuroectodermal tumour	Cerebral hemispheres	4	5
	Atypical teratoid or rhabdoid tumour	Throughout the brain	4	1
Glial tumours: arise from glial (supporting) cells	Astrocytoma	Throughout the brain	Pilocytic astrocytomas: 1; pilomyxoid astrocytomas: 2; anaplastic astrocytomas: 3; glioblastoma multiforme: 4	45
	Oligodendroglioma	Cerebral hemispheres	Oligodendroglioma: 2; anaplastic oligodendroglioma: 3	4
	Ependymoma	Throughout the ventricular system	Ependymoma: 2; anaplastic ependymoma: 3	10
	Choroid plexus tumours	Choroid plexus (within lateral ventricle)	Choroid plexus papilloma: 1; choroid plexus carcinoma: 3	2
Neuronal and glioneuronal tumours: arise from nerve cells	Ganglioglioma	Throughout the brain	1	3
	Dysembryoplastic neuroepithelial tumour	Cerebral hemispheres	1	2
Pineal parenchymal tumours: arise from melatonin secreting cells in the pineal glands (pineocytes)	Pineoblastoma	Pineal gland	2	1
	Pineocytoma	Pineal gland	4	1
Germ cell tumours: arise from germ cells that have become mislocated during embryonic development	Germinomas	Throughout the midline brain—for example, pituitary and pineal regions, hypothalamus, and third ventricle	Not included in WHO grading	4
	Teratomas			
	Embryonal carcinoma and yolk sac tumours			
Other developmental tumours	Craniopharyngioma	Epithelial tumour of sellar region (arises from Rathke's pouch epithelium)		
Meningiomas: arise from meningeal cells	Meningioma	Throughout the meninges	Meningioma: 1; atypical meningiomas: 2; anaplastic meningiomas: 3	2

*WHO=World Health Organization.

symptom onset and diagnosis. In a retrospective four centre cohort study of 139 children with a brain tumour, an average of one symptom or sign was reported at symptom onset, but this increased to six at the time of diagnosis.[14]

Figure 1 shows the combinations of symptoms and signs at diagnosis caused by tumours developing in different parts of the brain and the frequency with which they occur.[15] This information was obtained from a meta-anlysis of the presenting symptoms and signs in 4171 children who were newly diagnosed with a brain tumour. Recognition of these specific combinations of symptoms and signs is an essential step towards diagnosis. Cerebellar tumours present with ataxia, nystagmus, head tilt, and poor coordination (www.youtube.com/watch?v=SwcQ0Tv_4Vw). At least 75% of cerebellar tumours obstruct the flow of cerebrospinal fluid through the aqueduct and into the fourth ventricle so also present with symptoms and signs of raised intracranial pressure (headache, vomiting, lethargy, increasing head circumference, papilloedema, reduced level of consciousness).

Central brain tumours present with reduced visual acuity and fields, wandering or roving eye movements in young children (owing to loss of visual fixation), and damage to the hypothalamic-pituitary axis. This last feature leads to abnormal pubertal progression (precocious, arrested, or delayed), growth failure, diabetes insipidus, and diencephalic syndrome in young children (emaciation despite normal energy intake). Central tumours may also obstruct the flow of cerebrospinal fluid, leading to symptoms and signs of raised intracranial pressure.

Brain stem tumours present with swallowing difficulties, facial asymmetry and squint (owing to lower cranial nerve damage), hemiplegia, poor coordination, and abnormal gait (owing to long tract involvement). Cerebral hemisphere tumours are least likely to cause neurological signs and often present with focal seizures; they can also cause hemiplegia or a more focal motor weakness.

The developmental stage and ability of the child can also alter the presentation of tumours. For example, at least 20% of midline tumours cause visual impairment owing to compression of the optic chiasm and optic tracts. Older children can recognise that visual loss is abnormal and have the language skills to express this. Younger children lack this ability and are good at navigating familiar environments, so they can develop marked loss before this is recognised. Similarly, raised intracranial pressure causes headache. Older children can describe this, but younger children are often not good at localising pain and don't have the language skills to describe headache; instead, they may appear unsettled, lethargic, or withdrawn. Table 3 shows the most common symptoms and signs of brain tumours in different age groups.

Red flag symptoms

Attempts to reduce delays in diagnosis of tumours have identified "red flag" symptoms and signs that trigger referral to a "fast track" investigation and diagnostic service in secondary care. A population based case-control study determined the predicative value of such symptoms and signs in identifying children with a subsequent diagnosis of cancer presenting to primary care.[16] The red flags were taken from National Institute for Health and Care Excellence (NICE) referral guidelines for suspected cancer.[17] Just over a quarter of patients diagnosed as having cancer had any red flag symptom recorded in the previous three months, and a third in the preceding year.

However, red flag symptoms also occurred in children and young people who did not have a tumour (1.4% in three months and 5.4% in 12 months). Occurrence of a red flag symptom or sign increased the likelihood of a cancer diagnosis from 0.35 to 5.5 in 10 000 children at three months and from 1.4 to 7.0 in 10 000 children over a year. Symptoms and

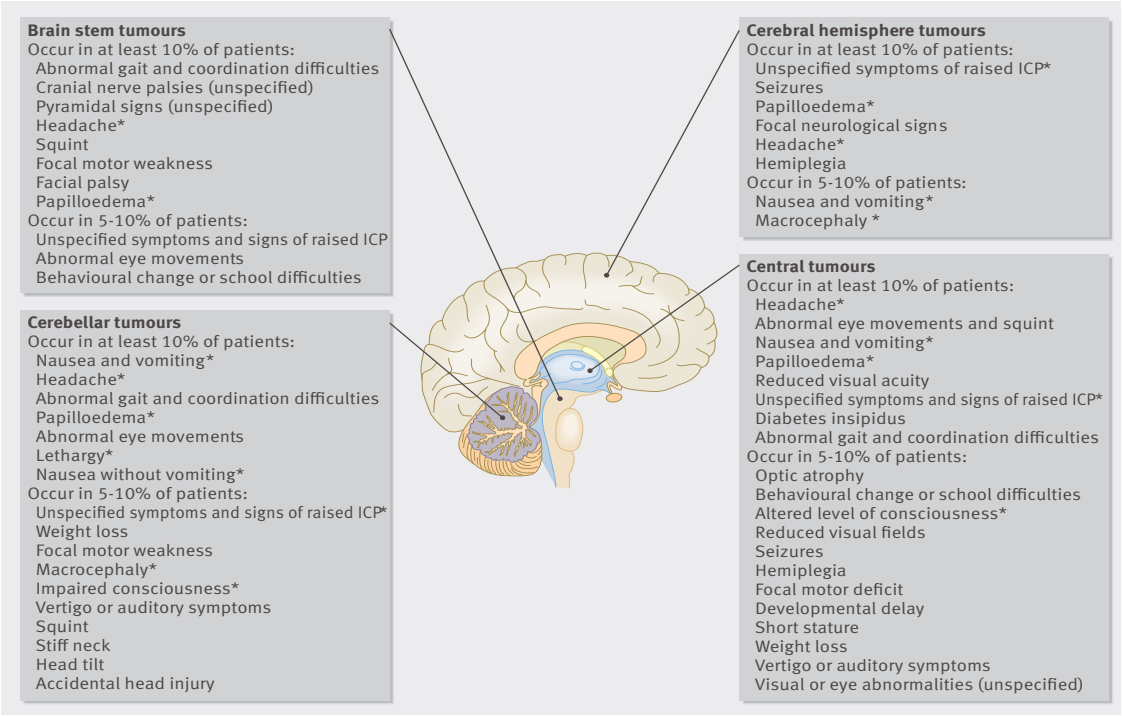

Fig 1 | Brain tumour presentation according to tumour location. *Symptom or sign caused by raised intracranial pressure (ICP)

signs with the highest predictive value for brain tumours were abnormal movement, visual symptoms, vomiting, headache, pain, and seizures.

Thus, red flag symptoms and signs do occur in brain tumours, but their lack of specificity limits their usefulness in identifying children and young people requiring rapid brain imaging to diagnose or exclude a brain tumour. Further evidence for this is provided by the routes to diagnosis study of all patients diagnosed as having cancer in England between 2006 and 2008, which found that only 2% of all childhood cancers were diagnosed through a "two week" wait referral.[18]

Cohort and case-control studies have shown an association between frequency of consultation and subsequent tumour diagnosis. The specificity of consultation frequency alone is low, but it is improved if combined with a red flag symptom. For example, of 10000 children attending their GP with visual symptoms within a three month period, six would be diagnosed as having cancer, but if they had consulted on three or more occasions (for any reason), this number increases to 23.[19] Referral should therefore be carefully considered for children with repeated consultations and a red flag symptom.

Table 3 | Brain tumour presentation according to age*

Pre-school (<5 years)	Primary school (5-11 years)	Secondary school (12-18 years)
Persistent or recurrent vomiting	Persistent or recurrent headache†	Persistent or recurrent headache†
Problems with balance, coordination, or walking	Persistent or recurrent vomiting	Persistent or recurrent vomiting
Abnormal eye movements	Problems with balance, coordination, or walking	Problems with balance, coordination, or walking
Behavioural change (particularly lethargy)	Abnormal eye movements	Abnormal eye movements
Fits or seizures (not with a fever)	Blurred or double vision†	Blurred or double vision†
Abnormal head position such as wry neck, head tilt, or persistent stiff neck	Behavioural change	Behavioural change
Progressively increasing head circumference†	Fits or seizures	Fits or seizures
	Abnormal head position such as wry neck, head tilt, or persistent stiff neck	Delayed or arrested puberty, slow growth†

*Based on a systematic review,[15] combined with clinical expertise and experience.
†Symptoms that differ according to age group.

What should I do if I suspect a brain tumour?

Include a brain tumour in the (often very wide) differential diagnosis of any child or young person presenting with the symptoms and signs shown in fig 1. Their presence should trigger a focused history (including family history and any predisposing genetic factors) and examination to look for corroborative findings (particularly the symptom and sign clusters associated with tumours in specific locations). Include motor and visual assessment, pubertal staging, and comparison of the child's height and weight with previous growth and age appropriate norms in the examination. It can be difficult to assess the visual function of pre-school children, so if necessary refer them to community optometry or ophthalmology. Children who present with symptoms of critical raised intracranial pressure (persistent headache and vomiting, confusion, drowsiness, reduced consciousness level) require urgent imaging of the central nervous system so, if in primary care, refer them the same day to local paediatric services.

The much harder management decision in both primary and secondary care is for children who appear reasonably well at assessment but who have a symptom or sign that could be caused by a brain tumour. In this situation, the clinician must decide whether no further action is needed and the family can be reassured; whether a period of watchful waiting and subsequent review is needed; or whether symptoms, signs, and additional examination findings are specific enough to merit referral for secondary care review or imaging.

A short period of watchful waiting can be helpful because symptoms and signs often evolve with time in children with brain tumours. Brain tumours however can progress rapidly, so review children who present with headache within four

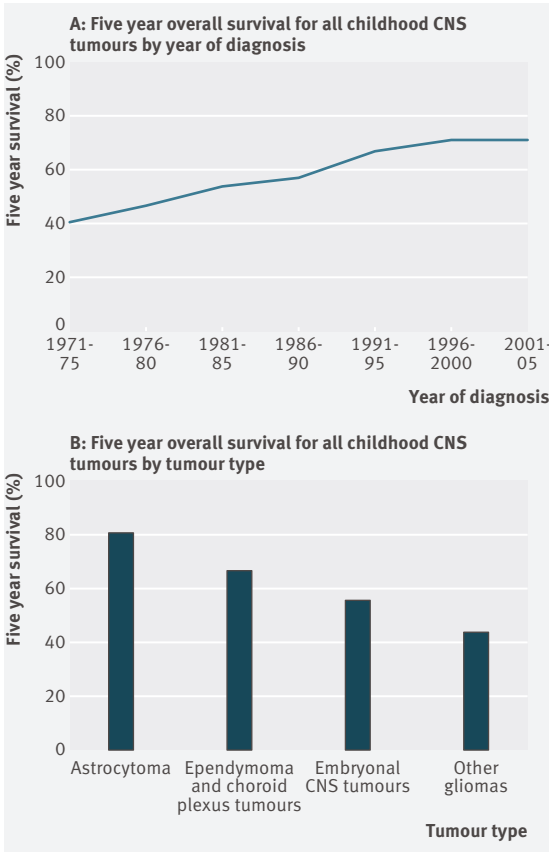

Fig 2 | Five year overall survival for childhood (age 0-15 years) brain tumours by year of diagnosis (A) and tumour type (B). [21 22]

weeks and those with all other symptoms and signs within two weeks. Tell parents and carers to return sooner if their child deteriorates. Book a follow-up appointment for young people at their initial consultation because they tend to be less reliable at returning with persisting symptoms.

NHS evidence endorsed clinical guidelines advising on assessment and indications for referral and imaging of children and young people who may have a brain tumour have been published.[20] The guidelines and other information sources are available on the HeadSmart website (www.headsmart.org.uk), which also advises on specific clinical situations where reassurance, review, or referral is an appropriate action.

How is a brain tumour confirmed?

Imaging of the central nervous system is needed to confirm or refute the diagnosis of a brain tumour. Imaging is used to confirm the presence of an intracranial mass lesion and to identify complications that require urgent intervention, such as the presence of a large mass effect or hydrocephalus. Both CT and magnetic resonance imaging (MRI) are suitable for this purpose. The widespread availability, ease of access, and speed of CT mean that this modality is widely used as first line imaging in children with suspected brain tumours. CT is particularly useful for emergency scanning of children who present in extremis, where time does not allow MRI, or for young children who would otherwise require general anaesthesia to undergo MRI in centres where access to general anaesthesia is limited.

However, in centres with good access to paediatric MRI services, MRI is used in preference to CT for children with suspected brain tumours. A brief protocol consisting of axial T2 weighted imaging can be used to effectively exclude a large intracranial mass lesion and takes around five minutes to perform. Full tumour MRI protocols may take more than an hour but provide both accurate anatomical localisation (including neuroaxis dissemination) and additional biological information, such as chemical composition, cellularity, and vascularity.

How are brain tumours treated ?

Brain tumours require multidisciplinary management, and the care of children and young people with brain tumours should be coordinated by their regional paediatric neurosurgery and neuro-oncology service. Treatment will be determined by the tumour type and location as well as the age of the child; it may involve surgery, chemotherapy, and radiotherapy. Research in paediatric neuro-oncology requires international collaboration, and patients are offered participation in clinical trials when available; our experience is that most families and young people welcome this opportunity.

Sequential clinical trials have led to great improvements in survival for many children and young people with brain tumours (fig 2).[21 22] However, survival varies greatly between different tumour types and locations. Recent progress in biotechnology has enabled identification of novel pathway aberrations in multiple tumour types and led to the search for novel anti-tumour agents that can act on these pathways.[23-25] Treatment of young children is particularly challenging because brain directed treatment can have a serious impact on the child's subsequent development. Current clinical strategies used to minimise the side effects of treatment include the use of intraventricular chemotherapy and proton radiotherapy.[26-28]

Rehabilitation and support for reintegration into education and society are essential. Children and young people should be assessed by neuropsychology, physiotherapy, occupational therapy, and speech and language services at diagnosis and ongoing care provided if needed. Return to education can be particularly challenging, and early communication with the child or young person's education provider to obtain advice on what support is likely to be needed facilitates this process. Children and young people treated with chemoradiotherapy for brain tumours often develop cognitive difficulties, particularly with the speed of processing, and it is important that this is recognised and supportive strategies implemented.[29 30] Children often require lifelong additional care, so early engagement with primary care is essential.

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