



**THE BRAIN PATHWAYS GUIDELINE:
A GUIDELINE TO ASSIST HEALTHCARE PROFESSIONALS IN THE
ASSESSMENT OF CHILDREN WHO MAY HAVE A BRAIN TUMOUR**

**Version 2 February 2017
(revision of version 1 Published 2008)**



NICE has renewed accreditation of the process used by the Children's Brain Tumour Research Centre, University of Nottingham to produce The Diagnosis of Brain Tumours in Children guideline. The renewed accreditation is valid until January 2022. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

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INTRODUCTION

1.2 Background

10 children are diagnosed with a brain tumour each week in the UK. Brain tumour symptomatology can be non-specific and can mimic other common childhood illnesses. The Brain Pathways guideline was initially written following evidence that many children in the UK were experiencing a prolonged total diagnostic interval (time from symptom onset to diagnosis; TDI), of a median of 14.4 weeks, compared to published international data [1]. It was felt that improved guidance for healthcare professionals could have an impact on this timeframe, enabling earlier diagnosis and reduced brain injury.

Whilst the NICE Referral Guidance for Suspected Cancer 2005 provided a concise summary of the common modes of brain tumour presentation, it had important methodological limitations. Firstly, it was predominantly directed at primary care clinicians whereas children with brain tumours experience diagnostic delay throughout the health service. Secondly, the “end-point” for the NICE guideline was referral. Brain tumours are diagnosed by imaging rather than referral and so guidance was required on indications for, and appropriate waiting times to, imaging. Finally, the guidance had a limited evidence base and was based upon an expert consensus without evidence review.

Following the publication of the guidance, the HeadSmart: Be Brain Tumour aware campaign (www.headsmart.org.uk) was launched as a public and professional awareness campaign to amplify the impact of the guideline. Data on the TDI has been collected across the UK and has shown a reduction from 14.4 weeks to 6.7 weeks in 2013 [3].

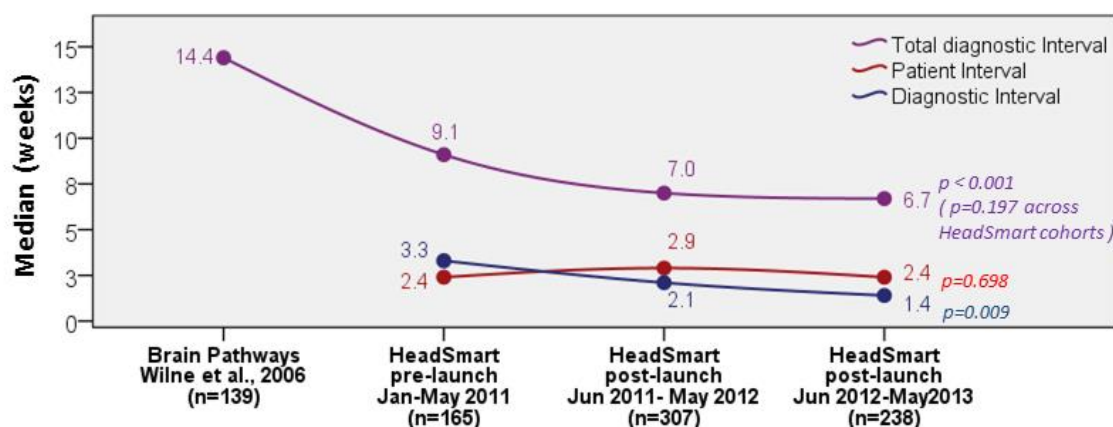


Figure 1: Comparison of HeadSmart key measures from 6 months before HeadSmart campaign launch (January 2011) to 2 years post-launch. Total diagnostic interval: time from symptom onset to diagnosis; patient interval: time from symptom onset to first presentation to health care professionals; and diagnostic interval, time from first presentation to health care to diagnosis [3].

Further analysis was conducted to identify subgroup(s) with prolonged total diagnostic intervals, with the intention of targeting the next phase of the awareness campaign towards particular patient and professional groups. The 12-18 group were found to have the longest delay with a median of 12.1 weeks, compared to 6 weeks for the 0-5 age group and 8 weeks for the 5-11 age group ($p < 0.001$) (Figure 2); and central tumours had the longest intervals compared to other locations, with a median total diagnostic interval of 10.5 weeks (Figure 3), median patient interval of 3.2 weeks and median diagnostic interval of 2.9 weeks.

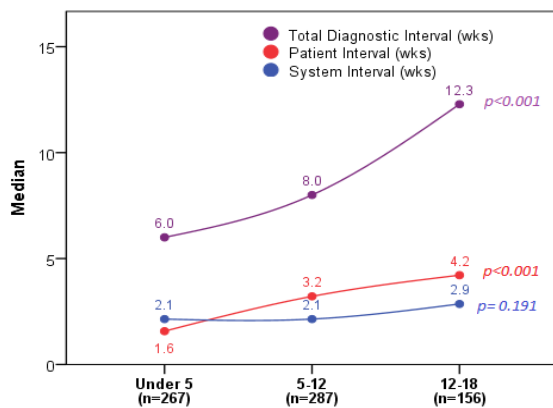


Figure 2: Total diagnostic interval, patient interval and system interval by age group

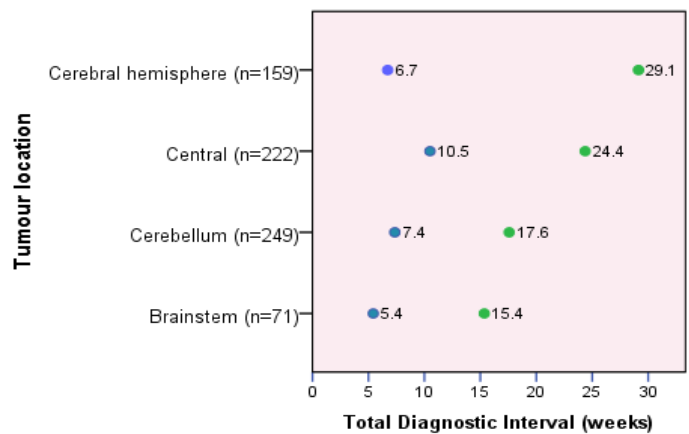


Figure 3 Total diagnostic interval by tumour location, ranked by difference between median (blue) and mean (green)

1.3 Aim of the guideline

This guideline aims to reduce the symptom interval experienced by children with brain tumours by providing evidence-based guidance for health professionals in

primary and secondary care on the following:

1. The symptoms and signs that may occur in children with brain tumours
2. Assessment of children presenting with these symptoms and signs
3. Indications and waiting times for imaging children with these symptoms and signs.

1.4 Clinical Health Questions

The guideline was devised to address the following clinical health questions:

1. What are the symptoms and signs that children with brain tumours develop?
2. Given that the initial symptoms and signs of a brain tumour may occur with other less serious childhood conditions, how can healthcare professionals distinguish those children who may have a brain tumour from the majority who do not?
3. What is the best way to clinically assess a child presenting with symptoms and/or signs that could be due to a brain tumour?
4. What symptoms and/or signs in children increase the likelihood of a brain tumour to the extent that their presence mandates brain imaging?
5. What is the best modality for brain imaging in children?
6. In a child who presents with symptoms and/or signs that could be potentially be due to a brain tumour, what is an appropriate maximum waiting time to imaging?
7. Are there specific presentations of childhood brain tumours that are repeatedly associated with diagnostic difficulty and a prolonged symptom interval?
8. Are there other barriers to diagnosis in childhood brain tumours and if so, how can these be addressed?

The clinical question used to direct our literature search was ‘**what are the symptoms and signs that children with brain tumours develop?**’

1.5 Scope and target population

Patient inclusion criteria: The guideline is applicable to all children aged 0-18 years who present with symptoms and/or signs that could result from a brain tumour and are being reviewed by a healthcare professional.

There are 94 recommendations in total with 48 strong recommendations. Levels of evidence and forms of recommendations are explained below and are taken from *SIGN*, Scottish Intercollegiate Guideline Network (2015). The recommendations and guideline has also been summarised into a “quick reference guide” for healthcare professionals (see Appendix 1).

1.5.1 Guideline users

1) Healthcare professionals

The guideline is intended to support the assessment and investigation by healthcare professionals of children who may have a brain tumour. It is applicable to any healthcare professionals who care for children in their clinical practice.

The guideline has been developed following careful consideration of the available evidence and has incorporated professional expertise via a Delphi consensus process. Healthcare professionals should use it to support their decision-making when assessing children who may have an intracranial tumour. It does not, however, override the responsibility of a healthcare professional to make decisions appropriate to the condition of individual children.

2) Parents and young people

The guideline has been summarized into age specific symptom cards (Appendix 2) designed to help parents and young people recognise signs and symptoms that could indicate a tumour and to support them in accessing appropriate assessment and investigation.

1.5.2 Views and preferences of the target population

The guidance was developed and revised using the same three-stage process that aimed to include all relevant stakeholders in guideline development. Stage one comprised collection of the evidence to support the guideline by way of a systematic review and meta-analysis of data. In stage two the evidence base was reviewed by a multi-disciplinary workshop; workshop members devised a series of statements from the evidence describing the clinical presentation, clinical assessment and investigation strategy for children who could have a brain tumour. In stage three the statements from the workshop were reviewed by doctors by means of a Delphi consensus process.

Parents of children who had been diagnosed with a brain tumour and lay representatives, as well as doctors from primary, secondary and tertiary care, were involved in the multi-disciplinary workshop; the parents and lay representatives were given specific time to voice their views and this was incorporated into the statements issued to the Delphi panel.

The Delphi panel included doctors from primary, secondary and tertiary care and included a wide range of specialties who may encounter children with these symptoms (general paediatricians, GPs, community paediatricians, paediatric gastroenterologists, CAMHS psychiatrists, emergency paediatricians).

The guideline development group (GDG) has also sent the revised draft guideline to four lay reviewers through our charity partner for comments. Two reviewers are young people in their early 20s and two are parents – one has children under 8, the other has grown up children. We

have incorporated their feedback into the revision

Members of the GDG, multi-disciplinary workshop and Delphi consensus group participants are listed in Appendix 3.

1.6 Levels of evidence and recommendation grades

Levels of Evidence

- 1++ High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
- 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- 1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2++ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, e.g. case reports, case series
- 4 Expert opinion

Forms of Recommendation

Judgement	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possible conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

Good Practice Points

Recommended best practice based on the clinical experience of the guideline development group

1.7 Stakeholder involvement

CBTRC and its charity partner, The Brain Tumour Charity (formerly known as Samantha Dickson Brain Tumour Trust; registered charity number. 1060627), are leading this review using shared funding sources. After the Guideline has benefitted from RCPCH and NICE review and feedback, it would be our intention to seek stakeholder involvement and approval using the stakeholder groups previously involved in assessing the original 2011 version and, in addition, a selection of groups who have formed in the meantime between the two versions. HeadSmart has a high

public, professional and political awareness; we would seek to sustain and enhance this awareness through involving stakeholders in consultation and dissemination

List of relevant stakeholders:

- Relevant professional colleges
- Other brain tumour charities
- Children's Cancer & Leukaemia Group (CCLG)
- National Institute for Clinical Excellence (NICE)
- Scottish Intercollegiate Guidelines Network (SIGN)
- All Party Parliamentary Group on Brain Tumours Chair: Rebecca Harris MP
- UK Parliamentary Petitions Committee. Chair: Helen Jones MP
- Specialty Commissioners NHSE

1.8 Funding

The initial guideline was funded by the Big Lottery Fund. The grant was applied for on behalf of the Children's Brain Tumour Research Centre by The Brain Tumour Charity. The grant for guideline implementation was awarded by The Health Foundation.

This revised guideline development process involving systematic review, Delphi process and planning of the professional campaign has been funded with prize money from the NHS Innovation Award awarded to the HeadSmart: Be Brain Tumour Aware campaign in 2013. The charity partner, The Brain Tumour Charity, has funded the public engagement and the implementation of the guideline through a publicity strategy involving professional and public champion network, a public and professional decision support website and other supporting material.

1.9 Conflicts of Interest (COI)

All GDG members, multidisciplinary workshop participants and Delphi consensus group participants were asked to declare any conflicts of interests (interests defined as in the Conflicts of Interest Policy set out by CBTRC see Appendix 4). Conflicts were reviewed and no relevant conflicts identified. The funders had no role in the guideline development and implementation process. Conflict of interest forms from all workshop and Delphi participants can be found in Appendices 5 and 6.

2. METHODS

2.1 Guideline development

The methodology for review consisted of a systematic review and meta-analysis, followed by a multidisciplinary workshop to discuss the evidence and a modified Delphi consensus process to finalise statements to include in the revised guideline.

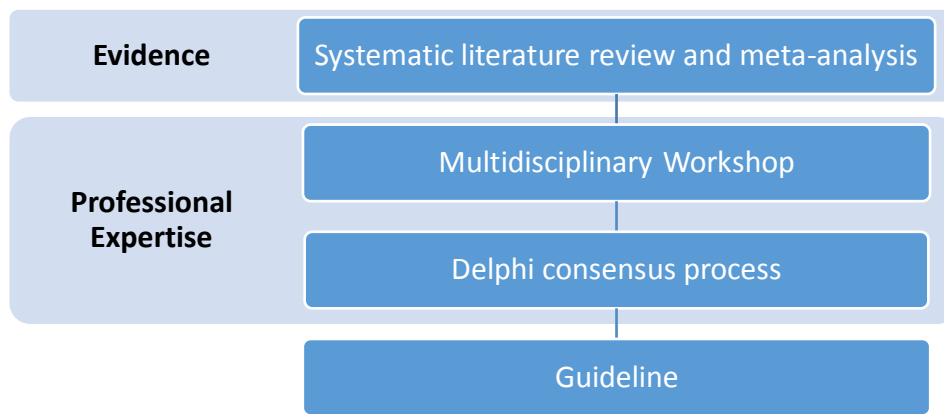


Figure 4. Guideline development methodology

The initial stage comprised appraisal of the currently available evidence on childhood brain tumour presentation and diagnosis. A systematic review and meta-analysis of the literature on childhood brain tumour presentation published between 2005 and 2015 was performed, which provided contemporary information and evidence regarding the presentation.

The questions of specificity, referral pathways, imaging indications and acceptable waiting times cannot easily be addressed by quantitative research methods. Qualitative methods in the form of a multi-disciplinary workshop and a Delphi consensus process were therefore employed to use professional expertise to incorporate the evidence from the meta-analysis and cohort study into a clinical guideline.

2.2 Systematic review and meta-analysis

Clinical Question: What are the symptoms and signs that children with brain tumours develop?

The previous systematic review and meta-analysis of the presenting signs and symptoms of childhood brain tumours was published in 2007 providing the initial evidence base for the development of this guideline [2, 3]. In order to update the guidance a second systematic review and meta-analysis was undertaken, using the same methodology as previously, for studies published from 2005 onwards in order to identify any changes in this field.

Identification of studies

MEDLINE, PubMed, and EMBASE were searched without language restriction, from January 2005 to August, 2015. Key words were: “brain tumour(s)”, “brain tumor(s)”, “brain neoplasm(s)”; and “diagnosis”; “presentation” and “sign(s)” or “symptom(s)”. Retrieved references were restricted to “human” and age (“infants”, “newborns”, “infant or child”, “preschool or child” and “adolescent”). For full search terms and strategy, see Appendix 7.

Papers with abstracts discussing tumour presentation, tumour diagnosis, or clinical symptoms and signs were retrieved for detailed review. 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 January 2005 were included. Conference abstracts were included if sufficient information was available from the abstract alone.

Exclusion criteria were papers (1) combined adult and paediatric data or no paediatric data; (2) had less than 10 children; (3) had insufficient detail about tumour presentation, tumour diagnosis, or clinical symptoms and signs; (4) had no primary data; (5) were duplicates or had unrelated

subject matter; (6) full text not available from British Library or interlibrary loan service.

Abstract of potentially eligible studies were screened by GDG members - 1 main reviewer and a sample of 200 was checked by another reviewer for quality assurance. A total number of 148 papers were included in the final analysis (Table 1); all non-English language papers were translated. [4-151].

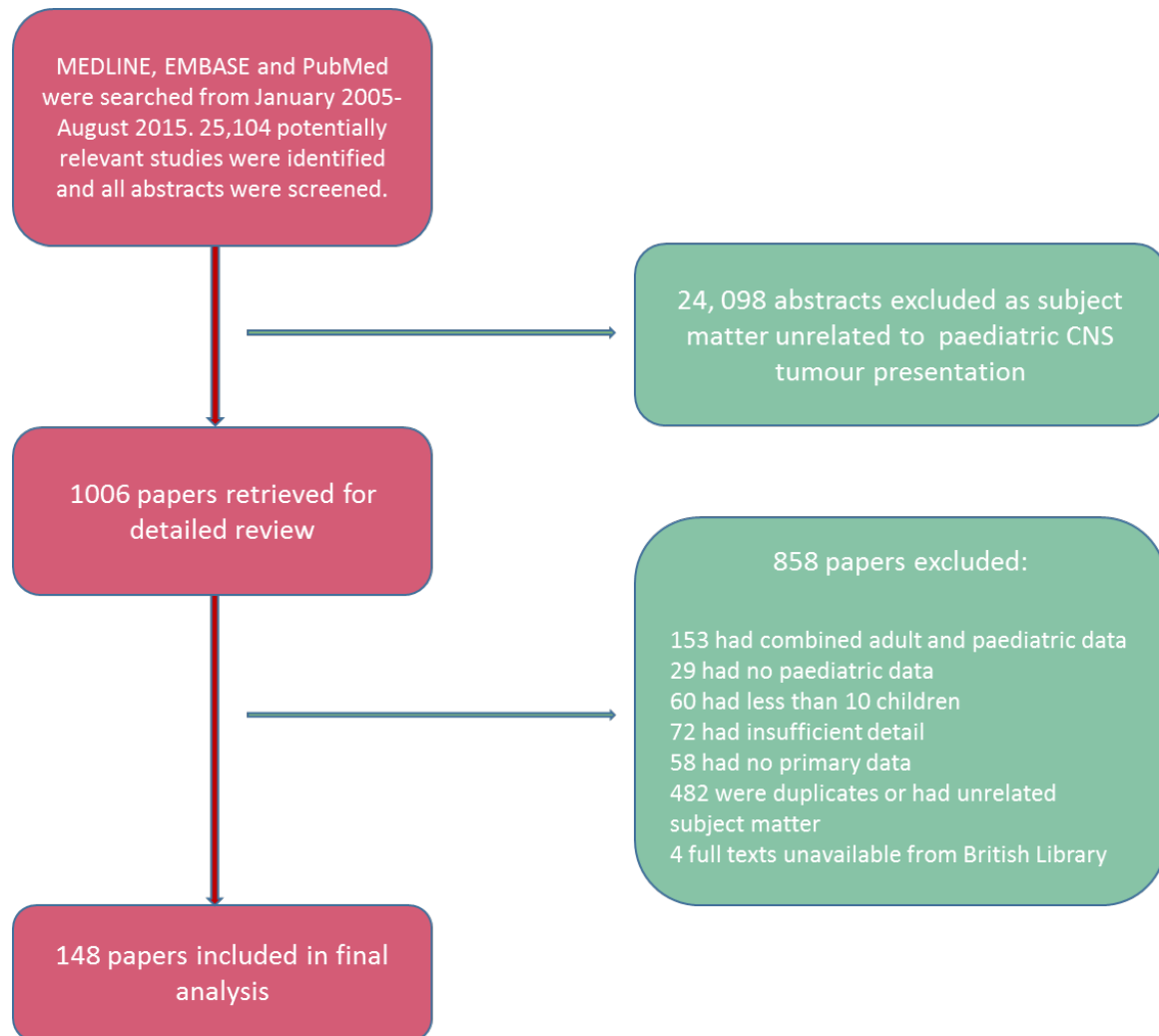


Figure 5: Progress through the meta-analysis

Data collection

Numbers of children in every study with a sign or symptom at diagnosis were recorded on a standard data extraction form. Information on signs and symptoms varied between studies; some studies had very detailed records on individual signs and symptoms (e.g. headache, vomiting, papilloedema), whereas others reported symptoms in clusters or complexes (e.g. visual disturbances or symptoms of raised intracranial pressure). Signs and symptoms were recorded as described in the individual studies. If a sign or symptom was not recorded in a study, it was assumed not to occur in that population. When symptoms clusters were non-specific and similar, they were grouped together (e.g. visual deficit, visual abnormalities, visual disturbances became visual /eye signs (NOS)).

Statistical analysis

Pooled proportions (%) of children with each sign or symptom at diagnosis were estimated using MetaXL version 5.3, a free shareware developed by Barendregt et al at the University of Queensland. The effect size (proportion) for each sign and symptom was calculated in the individual studies and weighted according to its variance. 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 pooled proportion. In MetaXL, proportions 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 analysis, heterogeneity was indicated beyond what could be expected by chance alone, by significant Q statistics and high inconsistency (I²) statistics. The random-effects model was selected because variability was expected across the papers, and a random-effects model was used.

Signs and symptoms occurring in 2% or more of the meta-analysis population are reported. 7 papers [7, 8, 11, 13, 27, 49, 75] reported combined categories, for example, “polyuria or polydipsia”, “seizure or movement disorder” which could not be re-classified into a single category. Since these papers reported detailed information for other signs and symptoms, they were included in the meta-analysis but excluded from the analysis of the combined signs or symptoms.

The following subgroup analyses were undertaken: All intracranial tumours; intracranial tumours in children aged under 4 years; posterior fossa tumours; central tumours (third ventricle, tectum, pineal gland, pituitary gland, thalamus, hypothalamus, optic pathway, and basal ganglia); and brainstem tumours. Only 2 papers described supra-tentorial tumours and therefore analysis was not deemed useful.

Analysis of all intracranial tumours was undertaken to provide a summary of paediatric intracranial tumour presentation. Children aged under 4 years cannot clearly describe symptoms such as headache, nausea, and diplopia, and therefore have a different presentation to older children. Analysis by tumour location was undertaken to highlight specific associations of signs and symptoms that occur with different tumour locations.

2.3 Multidisciplinary workshop

Following the systematic review and meta-analysis, it was necessary to incorporate professional expertise into guideline development in order to determine the specificity of signs and symptoms associated with childhood brain tumours and to advise on appropriate referral pathways, imaging indications and acceptable waiting times.

Revision multidisciplinary workshop

16 healthcare professionals and parents of children with brain tumours attended the workshop (Appendix 3). The workshop was chaired by members of the Guideline Development Group.

The workshop panel reviewed the existing guideline and new data obtained from the meta-analysis and examined the following signs, symptoms, management decisions and risk factors identified by literature review and previous guideline development team as being key to the diagnosis:

- Best practice
- Predisposing factors
- Headache
- Nausea and vomiting
- Visual symptoms

- Motor signs and symptoms
- Growth and development
- Behaviour
- Head circumference

For the new symptom of increasing head circumference, the group was asked to devise statements on the following:

- How would the signs and symptoms present to a healthcare professional?
- How should a healthcare professional assess a child presenting with this sign or symptom?
- How should a healthcare professional determine whether the presenting signs and symptoms could be due to a brain tumour, i.e. their specificity?
- What factors influence the specificity of a sign and symptom?
- What are appropriate thresholds for referral and selection for imaging for a child presenting with this sign or symptom?
- What would they regard as best practice for referral and imaging of a child presenting with this sign and symptom?

The discussion was recorded and contemporaneous notes made.

These discussion points were translated into a series of statements by the guideline development group at the end of the workshop and sent back to the workshop participants to ensure they reflected the discussion.

The workshop was approved by RCPCH for 5 CPD points, in accordance with the current RCPCH guidance.

2.4 Delphi process

A Delphi process is a means of developing a consensus between individuals. It provides a structured method of consultation that minimises bias. A Delphi process involves a series of sequential questionnaires interspersed by controlled feedback that seek to assess the extent of agreement (consensus measurement) and resolve disagreement (consensus development) among a group of experts [22]. The Delphi process aims to maximise the benefits from consulting a large number of experts over a short period of time while minimising the disadvantages associated with more traditional collective decision making processes e.g. committee meetings or steering groups.

A Delphi process requires the selection of a Delphi panel, the presentation of the information that the panel is to review as a series of statements and the setting of a consensus level i.e. the level of agreement required for a statement to be deemed as agreed upon by the Delphi panel. The statements are sent to the Delphi panel members and they are asked to rank their agreement with the statements (usually by means of a 9 point Likert scale) and to comment on the statements, particularly those with which they disagree. The rankings for each statement are collated and any statement that has achieved the pre-determined level of consensus is accepted. The results of the rankings are returned to the Delphi group. In a modified Delphi process (usually undertaken in guideline development) statements which have not achieved consensus are modified in light of the feedback received from the Delphi panel and reissued. This process is continued until all statements have achieved consensus or until feedback suggests that consensus is not going to be achieved.

A Delphi process therefore enables free discussion of views, allows individuals to change their personal opinion, can involve all groups with an interest in the area under review and can be completed within a reasonable time frame. A credible Delphi process must include a clear decision

trail that defends the appropriateness of the method to address the problem selected, the choice of expert panel, and the consensus level selected [153]. With these included, it is a practical and validated method for guideline development [154, 155].

Methods

Statements for the first round of the Delphi consensus process were derived from the statements developed by the multidisciplinary workshop and from the evidence base provided by the systematic review. Statements in the guideline that were agreed to be valid by the workshop group were not included in this Delphi consensus process. Only statements in the guideline which caused discussion and/or confusion were amended and included for consensus.

Emails of invitation to join the Delphi panel were sent to health specialists fulfilling one or more of the following criteria (for Delphi panel composition, see Appendix 3):

- Children's Cancer and Leukaemia Group (CCLG) member from one of the following disciplines: neurosurgeon, neuro-oncologist, neuro-radiologist, neurologist, neuro-endocrinologist or paediatric oncologist, UKCCSG Brain Working Group member and clinician.
- A range of general practitioners, paediatric gastroenterologists, paediatric emergency physicians, community paediatricians and psychiatrists across the UK.

Panel members were blind to the composition of the rest of the panel. The first and second of the Delphi Questionnaire was sent to panel members on 11 June and 7 August 2016 respectively. Panel members were asked to rate each statement on a 9-point scale from strongly disagree (0) to strongly agree (9). A comments section was included for each statement. Statements were taken as having reached consensus if 75% or more of the Delphi Panel respondents rated the statement 7, 8 or 9. Statements were rejected if 25% or less of the Delphi Panel respondents rated the statement 7, 8 or 9. Statements not reaching consensus were rewritten following review of comments from the Delphi panel and the revision multi-disciplinary workshop members then re-issued in subsequent rounds.

The questionnaire also asked the panel members to declare any conflicts of interests in order to ensure that the guideline development group could exclude or minimise any conflicts.

3 RESULTS

3.1 Systematic review and meta-analysis

The search strategy identified 25,104 abstracts. Of these, 1006 abstracts were selected and retrieved for full paper review, however 3 of these were not available from the British Library and so were excluded. 148 studies met inclusion criteria, describing signs and symptoms in 8714 children. A total of 149 signs and symptoms were recorded in total, however only those that occurred in 2% or more of the studied population are reported in Figures 6 and 7.

All cases

148 studies (n=8714) [4-151] described the signs and symptoms at diagnosis for children who had an intracranial tumour of any type or location (AC; all cases). These were (in decreasing order of frequency): headache (23%), nausea and vomiting (13%), signs of raised intracranial pressure (12%), unspecified visual or eye signs (10%), seizures (6%), motor weakness and deficit (5%), cranial nerve palsies (5%), ataxia (4%), hydrocephalus (3%), papilloedema (3%), increased head circumference/macrocephaly (3%) and focal neurological deficits (3%) (Figure 6). Other symptoms occurred in 2% of the population included gait/coordination abnormalities, cerebellar dysfunction/syndrome, endocrinopathy (including hypo-pit/pituitary dysfunction), lethargy,

hemiparesis, change in behavioural or educational performance, abnormal eye movement (nystagmus, Parinauds) and diplopia.

All brain

68 studies (n=5669) [5, 6, 8-10, 16, 18, 21, 23, 25, 27, 29, 31, 36, 38, 42, 47, 49-51, 54, 57, 59, 60, 63, 69, 70, 72, 74, 75, 77, 78, 80, 83-86, 90, 93-95, 98, 99, 101, 102, 105, 108-111, 113, 114, 117, 119, 121, 122, 126, 129, 130, 132, 134, 138, 139, 141, 147, 148, 150, 151] described the signs and symptoms at diagnosis for children with all brain tumours, i.e. their cohorts were not specific to one location (AB; all brain tumours). These were (in decreasing order of frequency): headache (19%), nausea and vomiting (17%), seizures (12%), signs of raised intracranial pressure (11%), unspecified visual or eye signs (8%), motor weakness and deficit (6%), increased head circumference/macrocephaly (5%), cranial nerve palsies (4 %), papilloedema (3%), hydrocephalus (3%), ataxia (3%), and focal neurological deficits (3%). Other symptoms occurred in 2% of the population include gait or abnormal coordination, lethargy, altered level of consciousness, change in behavioural or educational performance and cerebellar dysfunction/syndrome. (Figure 6)

Under 4s

17 studies (n=501) [16, 21, 25, 27, 38, 47, 50, 51, 75, 80, 85, 113, 122, 138, 139, 148, 151] were included in the analysis of children with intracranial tumours aged under 4 years. Ranked signs and symptoms, by pooled proportion at diagnosis were: increased head circumference/macrocephaly (21%), signs of raised intracranial pressure (11%), seizures (11%), nausea and vomiting (11%), hydrocephalus (7%), motor weakness and deficit (7%), unspecified visual or eye signs (4%), focal neurological deficits (4%), irritability (4%), lethargy (3%), cranial nerve palsies (3 %). Other symptoms occurred in 2% of the population are poor appetite, hypertonia/hypotonia, cerebellar dysfunction/syndrome, bulging/full fontanelle, torticollis/head tilt and seizure/movement disorder. (Figure 2)

Over 4's

17 studies (n=438) [19, 34, 42, 55, 61, 85, 88, 103, 107, 108, 126, 127, 128, 132, 142, 143, 148] were included in the analysis of children with intracranial tumours aged 4 years or older. Ranked symptoms and signs, by pooled proportion at diagnosis were: headache (34%), unspecified visual or eye signs (17%), menstrual irregularities (7%), galactorrhea (5%), endocrinopathy including hypo-pit/pituitary dysfunction (5%), nausea and vomiting (5%), polyuria and polydipsia (5%), growth problem including short/tall stature (5%), Cushing's syndrome (4%), accelerated development (4%), diabetes insipidus (4%), visual field defect (3%), visual loss or blindness (3%), and overweight (3%). Other symptoms occurred in 2% are decreased visual acuity, delayed puberty, acromegaly, hemiparesis, obesity, diplopia, amenorrhoea, galactorrhoea, motor weakness or deficit, intracranial pressure, hydrocephalus, precocious puberty, pituitary apoplexy, seizures and somnolence.

Location

10 studies (n=672) [4, 7, 20, 64, 68, 91, 96, 115, 116, 131] described children with posterior fossa tumours; 2 studies (n=58)[45, 133] described children with supratentorial tumours; 56 studies (n=1896)[12-15, 19, 22, 24, 26, 28, 32-35, 37, 40, 41, 43, 44, 46, 48, 52, 53, 55, 56, 61, 62, 65, 67, 71, 73, 76, 79, 81, 82, 87-89, 92, 103, 104, 107, 112, 118, 120, 123, 127, 128, 136, 137, 140, 142-

146, 149] described children with central tumours; 11 studies (n=409)[11, 30, 39, 58, 66, 97, 100, 106, 124, 125, 135] described children with brainstem tumours (Figure 7).

Table 1: Studies meeting inclusion criteria

Recruitment period	No of pts	Patient group, diagnosis if known, source of data	Tumour location	Mean age (yrs)	Median age (yrs)	Age range (yrs)	Median symptom interval / months	Mean symptom interval / months	Symptom interval range/months	Ref
2000-2011	66	Posterior fossa tumours 1I	PF	7.5	NS	NS	1.5	4.0	NS	[4]
1996-2004	330	All brain tumours 1I	AB	8	NS	NS	NS	7.7	0.01-108	[5]
2004-2009	46	All in Danish Cancer registry and regional patient registry	AB	NS	8.4	0.16-17.4	2.2	NS	0-24.3	[6]
1990-2005	166	Medulloblastomas 2I	PF	NS	6	NS	2.1	NS	0.1-15.2	[7]
1995-2008	60	All brain tumours 2I	AB	NS	5.8	0.12-15	0.7	NS	NS	[8]
2005-2008	152	All brain tumours 2I	AB	NS	8.5	0-16	2	NS	0-13.3	[9]
1994-2011	33	Memory and germ cell tumours	AB	13.5	NS	NS	NS	NS	NS	[10]
1997-2002	27	Brainstem gliomas; diffuse and non-diffuse 1I	BS	7.0 6.7	NS	NS	NS	2.61 10.58	NS	[11]
1985-2002	52	Craniopharyngioma 1I	C	9	NS	1.6-15.8	12.5	19.2	0.3-144	[12]
1990-2005	87	Craniopharyngioma 8I	C	10.2	NS	1.6-18	NS	NS	NS	[13]
1991-2002	12	Tectal gliomas 1I	C	6.75	NS	0.12-16	NS	NS	0.06-108	[14]
1988-2004	12	Pineoblastomas 1I	C	7	NS	0.5 - 18	NS	0.9	0.16-5.3	[15]
1997-2001	20	Under 3 years 1I *	AB	NS	NS	0.5-2.9	NS	4.36	0.03-17	[16]
1991-2006	10	Infratentorial gangliogliomas 1I	PF, BS	8.2	NS	2-16	NS	28.8	2- 84	[17]
2000-2007	34	Meningiomas 1I	AB	NS	10	2-17	2	NS	0.25-84	[18]
1996-2000	14	Germinomas from basal ganglia and thalamus 1I	C	12.4	NS	8-18	NS	NS	NS	[19]
1988-2003	30	Cerebellopontine angle tumours, 1I	PF	12.9	NS	0.12-18	NS	NS	NS	[20]
1974-2008	18	Intracranial tumours first year of life, 1I*	AB	5.5	NS	0-10	NS	0.75	0-2	[21]
1981-2010	176	Hypothalamic-pituitary lesions, 1I	C	NS	5.1	NS	3.6	8.4	NS	[22]
2004-2006	139	All brain tumours, 4I	AB	NS	8.1	0.08-16.7	3.3	NS	0-82.8	[23]
1989-2008	13	Craniopharyngioma, 1I	C	9.55	NS	2.9-15.1	NS	NS	NS	[24]
1995-2009	22	Under 1 yr* 1I	AB	NS	0.29	0-0.99	NS	NS	0.03-2	[25]
1988-2008	18	Choroid plexus tumours, 1I	C	4.6	NS	0.25-16.9	2.3	NS	0-1	[26]
1998-2007	16	Brain tumours in children <6m*, 1I	AB	NS	0.43	0.1-0.5	NS	NS	NS	[27]
1985-2004	39	Craniopharyngiomas, all of denmark	C	NS	NS	NS	NS	NS	NS	[28]
1995-2011	65	Glioblastomas, 1I	AB	13.29	NS	2-18	NS	4.79	0.01-60	[29]
2004-2009	33	Brainstem tumours, 1I	BS	9.8	9	3-15	2	NS	0.5-6	[30]

2000-2010	46	CNS tumours, 1l	AB	NS	8	1-17	2	NS	NS	[31]
1990-2010	10	Craniopharngioma 1l	C	9.4	NS	2.4-17.6	NS	NS	NS	[32]
1998-2011	42	Optic pathway gliomas, 1l	OP	7.25	5.58	1.08-16.6	NS	NS	NS	[33]
2001-2011	12	Giant pituitary adenomas, 1l	C	14.3	NS	12-18	NS	NS	NS	[34]
1989-2003	69	Thalamic tumours, 1l	C	9.5	NS	0-16	NS	4.9	0.06-36.4	[35]
2006-2012	15	Intracranial atypical teratoid rhabdoid, 1l	AB	NS	5	0.8-8	2	NS	0.5-6	[36]
1991-2012	34	Astrocytomas, 1l	C	8	NS	1-17	NS	7.5	NS	[37]
1985-2008	27	First 120 days of life*, 1l	AB	NS	0.18	0-0.3	NS	NS	NS	[38]
1980-2010	65	Brainstem tumours, 1l	BS	8	NS	1.1-17.6	2	6.3	0-108	[39]
1993-2012	23	Choroid plexus tumours, 1l	C	NS	1.5	0.25-15.8	NS	NS	NS	[40]
1994-2010	15	Meningiomas, 1l	AB	12	NS	4-18	NS	12	2-36	[41]
2009-2014	56	Pituitary tumours >10yrs of age*, 1l	C	16.6	NS	10-18	NS	NS	NS	[42]
2004-2012	20	Craniopharyngiomas, 1l	C	7.3	NS	1.25-13.75	NS	6	1-36	[43]
1998-2013	23	Supratentorial, 1l	ST	4.5	NS	0.08-16.5	NS	NS	NS	[44]
1999-2011	17	Craniopharyngiomas, 1l	C	9	NS	4-18	NS	NS	NS	[45]
2008-2012	21	Brain tumours, under 3YR*, 1l	AB	NS	0.45	0.2-1.5	NS	NS	NS	[46]
1998-2007	10	Tectal plate tumours, comparison <10 and >10* 1l	C	10.6	NS	0.9-18	NS	<10= 0.5 >10 = 18	<10 = 0.25-1 >10 = 12-30	[47]
2002-2008	99	Brain tumours, 1l	AB	7.4	NS	NS	NS	NS	NS	[48]
1979-2005	33	CNS tumours in <6m*, 1l	AB	0.25	0.24	0-0.5	NS	NS	NS	[49]
1992-2007	10	Diffuse pontine glioma in <3yr olds*, 1l	AB	NS	2.2	0.8-2.7	2.5	NS	0.75-18	[50]
1988-2004	14	Pure pineal germinomas, 1l	C	NS	12	0.5-18.1	NS	NS	NS	[51]
1982-1999	33	Optic Pathway gliomas, 1l	OP	8.3	NS	NS	NS	NS	NS	[52]
1988-2001	200	Brain tumours, 2l	AB	7.4	NS	0.28-17	2.5	NS	0-10	[53]
1992-2003	16	Thalamic tumours, 1l	C	7.4	NS	2.4-14.9	NS	NS	NS	[54]
1991-2001	42	Pituitary adenoma, 1l	C	15.6	NS	9-18	NS	NS	NS	[55]
1990- 2005	10	Atypical teratoid rhabdoid tumor, 1l	AB	3.15	1.92	0.25-7	1	1.3	NS	[56]
2000-2008	20	Brainstem tumors, 1l	BS	7.95	NS	2-13	NS	6.59	0.5-60	[57]
1997-2007	18	Intracranial ependymoma, 1l	AB	NS	NS	0.5-15	NS	NS	1-47	[58]
2001-2011	12	Intracranial teratomas, 1l	AB	NS	NS	0-16	NS	NS	NS	[59]
1984- 2003	40	Tectal plate, 1l	C	NS	9.4	0-17.6	NS	8.5	NS	[60]
1985-2005	11	Germ cell tumors in basal ganglia, 1l	C	CD	CD	7-16	CD	CD	CD	[61]
1974-2005	18	Meningiomas, 1l	AB	12.8	NS	0.75-18	14.4	NS	NS	[62]
1988-2006	142	Posterior fossa tumors, 1l	PF	5.2	NS	0.4-16	NS	NS	NS	[63]
1984-2004	14	Thalamic gliomas, 1l	C	8.1	NS	2-15	NS	4.8	1-10	[64]

1995-2003	14	Brainstem tumors, 1l	BS	NS	4.8	2.4-11.4	NS	1.65	0.25-4	[65]
1982-2002	35	Craniopharyngiomas, 1l	C	7.4	NS	NS	12	NS	0-132	[66]
2000-1006	23	Medulloblastoma, 1l	PF	7.52	NS	2-13	NS	NS	NS	[67]
1974-2010	104	Primary meningiomas, 1l	AB	NS	11	0.41-17	NS	NS	1-60	[68]
2005-2008	445	All tumours, 4l	AB	NS	NS	2-14	NS	NS	NS	[69]
1998-2010	13	Choroid plexus tumours, 1l	C	NS	NS	0-14	NS	NS	NS	[70]
2011-2011	192	All brain tumours, evaluation of headsmart, 18l	AB	NS	6.3	0.11-16.9	2.1	NS	0-99.5	[71]
1998-2008	38	Choroid plexus tumours, 1l	C	13.13	3.54	NS	NS	NS	NS	[72]
2007-2011	117	Brain tumours, 1l	AB	8.7	NS	0-18	NS	NS	NS	[73]
2003-2013	32	Brain tumors 2yrs and under, 1l*	AB	NS	1.33	0-2	NS	1.73	0.5-4	[74]
1983-2013	77	Macroprolactinomas in children, 1l	C	16.1	NS	4.5-20	NS	NS	NS	[75]
2000-2013	142	All brain tumours, 1l	AB	8.1	8	NS	0.66	4.7	0-36	[76]
1980-2004	245	Brain tumors, 1l	AB	NS	6.83	0-19.2	0.8	NS	0-26.1	[77]
1999-2012	45	Thalamic tumors, 1l	C	11.06	NS	3-19	NS	0.8	0.16-2.6	[78]
2006-2010	87	Brain tumors under 3 yr olds, 1l*	AB	NS	NS	0-3	NS	NS	NS	[79]
1990-2010	39	Paediatric thalamic tumors, 1l	C	NS	NS	NS	NS	NS	NS	[80]
1954-2008	82	Craniopharyngiomas, 1l	C	NS	NS	0-15	NS	NS	NS	[81]
2001-2010	34	Astrocytomas, 1l	AB	NS	10	0-18	6.05	NS	NS	[82]
1999-2009	80	CNS tumours, 4l	AB	10.2	NS	NS	NS	NS	NS	[83]
1996-2011	87	Intracranial tumors under 3 yrs of age, 1l*	AB	1.66	NS	0-3	NS	NS	NS	[84]
2002-2014	39	Prolactinomas, 1l	C	NS	NS	11-19	NS	NS	NS	[85]
1995-2013	15	Ventral midbrain tumours, 1l	C	6.9	NS	NS	NS	14.2	0.5-108	[86]
1999-2013	420	Pediatric CNS tumors, 1l	AB	NS	NS	NS	NS	4.9	NS	[87]
2013	22	Childhood prolactinomas, 1l	C	NS	NS	6-18	NS	NS	NS	[88]
2000-2012	20	Craniopharyngiomas, 1l	C	NS	7	NS	NS	NS	NS	[89]
1992-2010	74	High grade CNS tumours, 1l	AB	NS	8.3	0-17	NS	NS	NS	[90]
1981-2011	84	Posterior fossa Tumors, 1l	PF	8.6	NS	1-14	NS	16	0-48	[91]
1995-2012	44	Tectal plate gliomas, 1l	C	10.2	NS	2-19	NS	NS	NS	[92]
1073-2012	30	Brain Tumours, 1 st 6 months of life, 1l*	AB	NS	NS	0-0.5	NS	NS	NS	[93]
1998-2008	79	Brain tumors, 1l	AB	9.2	NS	0.2-23.5	3.5	6.9	0-74.85	[94]
1995-2007	22	Pilocytic astrocytoma, 1l	AB	9.25	NS	1-15	NS	NS	NS	[95]
2005-2012	89	Medulloblastomas above 3yrs, 1l*	PF	NS	6	0.81-13.21	NS	NS	NS	[96]
2005-2013	73	DIPG	BS	8.66	8	2.25-17.9	NS	NS	1.25-6	[97]
1954-2008	1143	Brain tumours, 1l	AB	NS	NS	0-14	NS	NS	1.1-6.8	[98]
2002-2011	87	Pediatric brain tumors, 1l	AB	8.7	NS	0.8-17	NS	NS	NS	[99]

1999-2013	24	Diffuse intrinsic pontine glioma, 1I	BS	NS	6.1	2.9-16.6	1.0	NS	0.5-5	[100]
1980-2010	186	Low grade gliomas, 1I	AB	NS	7.4	0.25-17.8	NS	NS	NS	[101]
1991-2005	13	Glioblastoma multiforme, 1I	AB	10.4	NS	0.25-20	NS	1.55	0-7.5	[102]
1981-2005	20	Pediatric adenomas, 1I	C	15.6	NS	8-19	NS	NS	NS	[103]
1997-2012	20	Craniopharyngiomas, 1I	C	10.1	NS	3-16	NS	NS	NS	[104]
2002-2012	172	Brain tumours, 1I	AB	6.5	NS	0-19	NS	NS	NS	[105]
1971-2004	48	Low grade brainstem gliomas, 1I	BS	NS	12	2.5-19.5	NS	NS	NS	[106]
1975-2012	39	Pituitary adenoma, 1I	C	15.3	16	6-18	NS	NS	NS	[107]
1998-2010	17	Intracranial germ cell tumours, 2I	AB	NS	13	8-29	2	NS	0-86	[108]
1994-2006	40	Pediatric brain tumors, 1I	AB	9.75	NS	1-15	NS	13.4	NS	[109]
1998-2005	13	Intracranial tumours, 1I	AB	4.6	NS	0.5-13	NS	NS	NS	[110]
1940-2004	20	Meningiomas, 1I	AB	NS	13	3-20	NS	NS	NS	[111]
1989-2006	18	Optic Pathway Hypothalamic Gliomas, 1I	OP	NS	5.5	0.25-16.5	NS	NS	NS	[112]
1996-2006	12	Congenital brain tumors, 1I	AB	0.14	NS	0-0.41	NS	NS	NS	[113]
1983-2007	21	Intracranial meningioma, 1I	AB	10.3	NS	2-16	NS	4.6	1-12	[114]
2004-2006	22	Cerebellar tumours, 1I	PF	7.1	NS	1.16-17	NS	NS	NS	[115]
2002-2005	40	Posterior fossa tumors, 1I	PF	8.31	NS	3.5-15	NS	8.1	NS	[116]
1996-2006	13	Intracranial meningiomas, 1I	AB	9.8	NS	1.8-15	NS	13	1-30	[117]
2013	47	Craniopharyngiomas, 1I	C	11.2	NS	NS	NS	NS	NS	[118]
2007-2012	39	CNS Tumor, 1I	AB	7	NS	0.83-17	NS	NS	NS	[119]
1981-2010	27	Craniopharyngiomas, 1I	C	NS	8.5	0-16	3	NS	NS	[120]
2007-2012	187	Brain tumors, 1I	AB	NS	NS	0-18	NS	NS	NS	[121]
1998-2012	25	Brain tumors in first year of life, 1I*	AB	NS	0.33	0-1	NS	NS	NS	[122]
1986-2012	19	Bithalamic tumors, 1I	C	NS	7.5	3-12	NS	NS	NS	[123]
1986-2010	52	Low grade brainstem tumors, 2I	BS	7.7	6.5	1-17	NS	NS	NS	[124]
2002-2013	11	Exophytic glioma of the medulla, 1I	BS	4.2	NS	0.91-7	NS	7.9	2-24	[125]
1990-2006	30	CNS germ cell tumor, 1I	AB	10.9	NS	6-17	NS	8.4	0-36	[126]
1993-2007	35	Pituitary adenomas, 1I	C	NS	15	7-18	NS	NS	NS	[127]
1997-2006	12	Immature teratoma, 1I	C	14.6	NS	8-28	NS	NS	NS	[128]
1994-2011	64	Subependymal giant cell astrocytoma in TSC, 1I	AB	9.7	NS	0-26	NS	NS	NS	[129]
2006-2009	15	Glioblastoma multiforme, 1I	AB	NS	10	4-17	NS	2	1-5	[130]
1991-2005	10	Medulloblastoma, 1I	PF	9	NS	1.4-15.1	NS	2.2	NS	[131]
1986-2006	13	Germ cell tumours, 1I	AB	12.9	NS	7-17	NS	NS	NS	[132]
1990-2004	35	Supratentorial oligodendrogliomas, 2I	ST	9.46	NS	0-15.25	NS	15.5	NS	[133]
1991-2001	14	Germ cell tumors, 1I	AB	12.2	NS	0-18	NS	NS	NS	[134]

1988-2006	42	Brain stem tumors, 1I	BS	6.36	NS	0.25-12	NS	NS	NS	[135]
1977-2004	73	Craniopharyngiomas, 1I	C	8.02	7	1.42-17.58	NS	NS	NS	[136]
1975-2006	24	Pineal tumours, 1I	C	NS	8.2	0.5-15.1	NS	NS	NS	[137]
(22yr period)	13	Congenital CNS tumors, 1I	AB	NS	NS	0-0.5	NS	NS	NS	[138]
2005-2008	21	Intracranial neoplasms under 1 yr, 1I*	AB	0.41	NS	0-1	NS	3	NS	[139]
1992-2008	17	Craniopharyngiomas, 1I	C	NS	12	4-18	NS	NS	NS	[140]
1983-2003	11	Meningiomas, 1I	AB	NS	NS	1.1-17	NS	NS	NS	[141]
2009	31	Craniopharyngioma, 1I	C	11.6	NS	7-14	NS	NS	NS	[142]
2011-2012	17	Craniopharyngioma, 1I	C	10.29	NS	5-14	NS	NS	NS	[143]
2006	29	Craniopharyngioma, 1I	C	9.1	NS	3-16	NS	NS	NS	[144]
1976-2004	32	Craniopharyngiomas, 1I	C	6.8	NS	0.3-13.3	NS	NS	NS	[145]
1997-2010	23	Pineal tumours, 1I	C	10.9	NS	0.33-18	NS	NS	NS	[146]
1997-2002	69	Brain tumors, 1I	AB	NS	NS	0-14	NS	NS	NS	[147]
1999-2004	50	Brain tumours, 1I	AB	NS	NS	0-16	1	5.75	NS	[148]
1982-2000	70	Hypothalamus-hypophysis tumours, 1I	C	9.7	NS	0.8-17	NS	NS	NS	[149]
1998-2004	81	Brain tumours, 1I	AB	8.7	8.1	0.125-17.2	NS	NS	NS	[150]
1997-2011	31	Brain tumours in infancy, 1I*	AB	6.7	NS	0-1	NS	NS	NS	[151]

1I=treated at one institution. 2I=treated at two institutions. 4I=treated at four institutions. 7I=treated at seven institutions, 8I=treated at 8 institutions. AB=all brain. NS=not specified. OP=optic pathway. C=central. ST=supratentorial. BS=brainstem. PF=posterior fossa. CD= combined adult and paediatric data therefore means and medians not included.

* Study population defined by age rather than tumour type or location

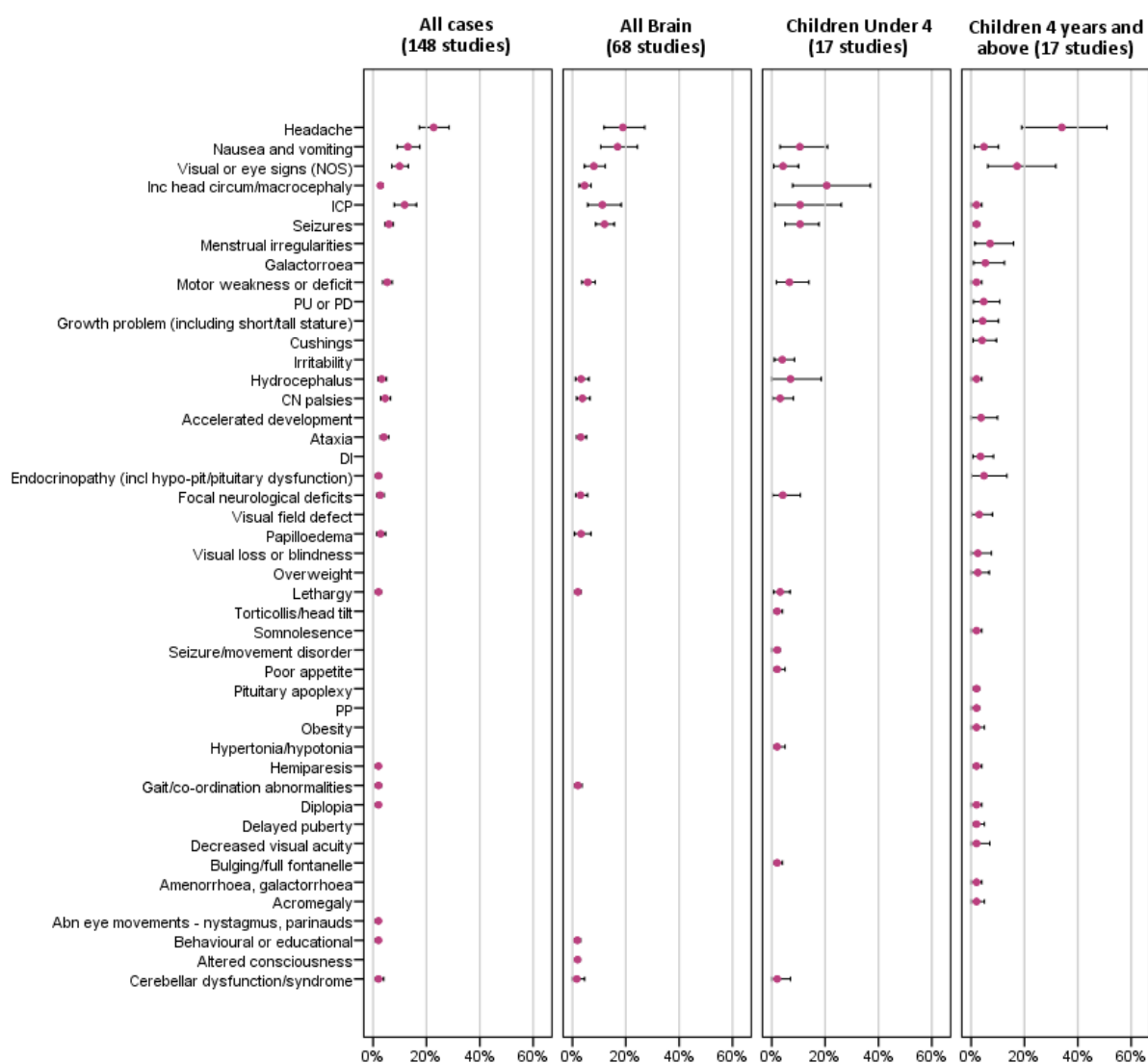


Figure 6: Frequency of symptoms and signs in children with intracranial tumours - analysis by age

ICP=intracranial pressure; NOS=not otherwise specified; CNP=cranial nerve palsy; PU/PD = polyuria and polydipsia; DI=diabetes insipidus; PP= precocious puberty

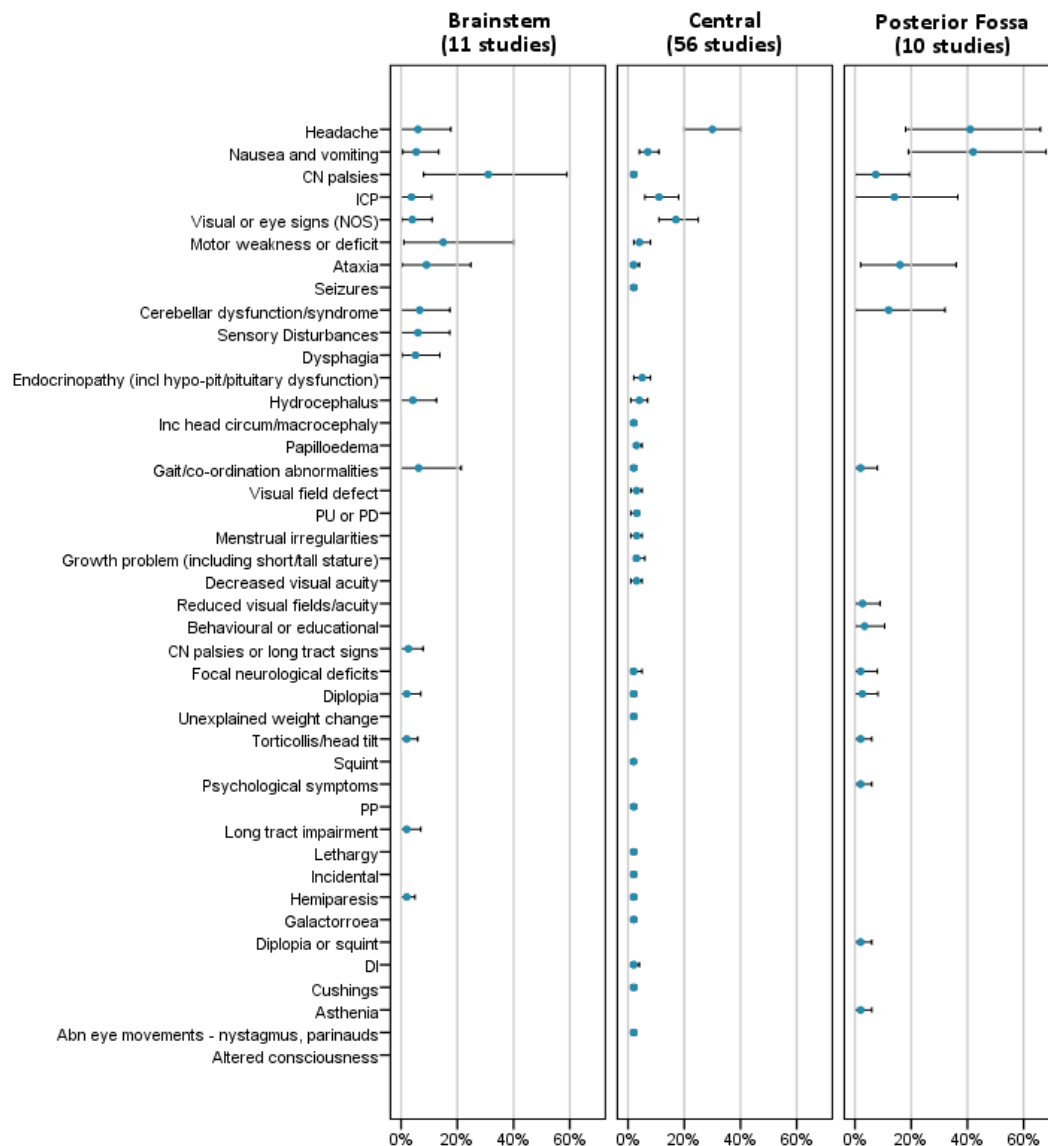


Figure 7: Frequency of symptoms and signs in children with a central nervous system tumour - analysis by tumour location

ICP=intracranial pressure; NOS=not otherwise specified; CNP=cranial nerve palsy; PU/PD = polyuria and polydipsia; PP= precocious puberty

3.2 Multidisciplinary workshop

Where the guideline development team decided that a discussion point should not be included in the guideline the reason is documented. Statements from the original guideline that were agreed to be valid by the workshop participants were not included in the modified Delphi consensus process, as they had previously reached consensus. Only areas of the guideline which caused discussion and/or confusion were amended and included for consensus.

Below is a summary of the workshop discussion and conclusions.

3.2.1 Consultation

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
Parents and their carers should be explicitly asked about their concerns in any consultation	Agreed
If parent/carers express concern about brain tumour should be taken seriously	C1
If brain tumour unlikely, reasons why need to be explained with reference to symptom card/decision support tool	C1
If patient/carers and HCP not fluent in common language then interpreter must be used	Agreed
If a child warrants review, new DoH guidance needs to be complied with	C2
Low parental educational level, social deprivation and lack of familiarity with UK healthcare system may be associated with diagnostic delay. MDT approach with HV input can help.	C4

3.2.2 Imaging

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
A child in whom CNS imaging is required to exclude a brain tumour (potential diagnosis but low index of suspicion) should be imaged within 4 weeks	IM1 – amended to include result as new DoH aim diagnosis or all clear within 4 weeks.
MR imaging is the modality of choice for making the diagnosis	Agreed
If MRI not available, contrast CT should be used	Agreed
Imaging results should be interpreted by a professional with expertise and training in CNS CT/MRI in children	Agreed
The need to sedate or anaesthetise a child should not delay diagnosis	IM2 – amended to take into account DoH guidance

3.2.3 Referral

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
A primary HCP who has a high index of suspicion regarding a possible brain tumour should discuss their concerns with a secondary HCP the same day.	Agreed
2 week wait does not work in children – only 2% of children seen end up having a cancer diagnosis.	R2
A child referred where brain tumour is in differential but low index of suspicion should be seen in a rapid-access clinic or similar setting	R2

3.2.4 Predisposing factors

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
Predisposing factors as listed in current guideline should be specifically asked about in consultation, as a checklist	C3

3.2.5 Headache

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
Consider a brain tumour in any child presenting with a new persisting headache	Majority of general paediatric clinic patients referred with headaches for months. Headache in isolation very rarely due to brain tumour. H1
A thorough assessment for other signs and symptoms important	H2
Brain tumour headaches can occur at any time of the day or night	Agreed
Children aged younger than 4 years, or those with communication difficulties, are frequently unable to describe headache; their behaviour is important	Agreed
In a child with a known migraine or tension headache a change in the nature of the headache requires re-assessment	Agreed
Patients identified with headache without clear cause should be followed up within 4 weeks	H3
An investigatory algorithm for headaches in children should be used	Beyond the scope of the guideline – but refer to NICE >12s
CNS imaging required for: persistent headache that wakes a child from sleep, persistent headaches that occur on waking, persistent headache occurring at any time <4s, confusion	Agreed
1 or more other symptoms with headache	This was agreed would warrant a scan – as it was previously on the symptom cards, not sent out to Delphi

3.2.6 Nausea and vomiting

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
Lots of babies and children referred with vomiting and unlikely to be a brain tumour	Not included as statement too general, no specific referral pathways recommended.
Persistent nausea/vomiting with another symptom from checklist requires MRI	NV1
Young children/babies tolerate raised intracranial pressure well as fontanelles open – would not complain of headache	NV2
Head circumference important to measure and monitor in young children with persistent vomiting	NV2
The history of persistent or recurrent nausea and/or vomiting without obvious cause should raise the consideration of a brain tumour	Agreed
Persistent vomiting on awakening requires CNS imaging	Agreed

3.2.7 Visual assessment

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
Consider a brain tumour in any child presenting with visual abnormality that is persistent	Agreed
Any parental concern about vision needs to be taken seriously, even if on your assessment you cannot readily see any concern	V1
Visual assessment must include assessment of: pupil responses, visual fields in school age children, eye movements, optic disc appearance, visual acuity	Agreed
If the assessing HCP is unable to perform full visual assessment, the child should be referred for assessment	Agreed
Children referred for visual assessment with signs or symptoms suggestive of a brain tumour should be seen within 2 weeks of referral	Agreed
Community optometry should refer any child with abnormal eye findings suggestive of a possible brain tumour directly to secondary care	Agreed
Consideration should be given to the appropriate place of assessment. If appropriate community optometry expertise is not available, pre-school and uncooperative children should be assessed by the hospital eye service.	Agreed

A child with new onset squint should have early ophthalmological assessment for consideration of underlying causes	Agreed
CNS imaging required for: papilloedema, optic atrophy, new onset nystagmus, reduction in visual acuity not attributable to an ocular cause, proptosis, new onset squint	Agreed
If there are abnormal eye findings together with progression of presenting non-ocular symptoms or additional symptoms, the child should be referred for imaging.	Agreed

3.2.8 Motor assessment

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
Consider a brain tumour in any child presenting with a persisting motor abnormality	Agreed
Brain tumours may cause a deterioration or change of motor skills	M1
Change in hand preference is not subtle. Subtle changes include computer games, handwriting	M1, M2
Cannot always observe all motor skills if child not compliant at the time, questioning can also be helpful as parents will be able to give accurate account	M3
CNS imaging is required for any child with persistent focal neurological signs	M4
CNS imaging required for: a regression in motor skills, abnormal gait/co-ordination with no other cause, focal motor weakness, swallowing difficulties with no local cause, abnormal head position	M4
Bell's palsy with no improvement should be imaging within 4 weeks	Agreed as would expect at least some improvement within 4 weeks

3.2.9 Growth and development

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
Height and weight should be measured at every contact with every HCP	GR1
Height or weight outside the normal range should be referred to secondary care	GR2
Consider a brain tumour in any child with 2 of: growth failure, delayed or arrested puberty, polyuria/polydipsia	Agreed

Early referral required for any of the above and galactorrhoea or amenorrhoea	GR3
Diabetes insipidus must be considered in a child presenting with polyuria and/or secondary enuresis	Agreed
Early specialist referral for consideration of underlying causes including CNS causes is required for a child presenting with precocious puberty	Agreed
Tumours affecting midline supratentorial part of brain can also affect vision	GR4
Atypical anorexia can be misdiagnosed when actually an underlying CNS tumour	GR5

3.2.10 Behavioural

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
A history of lethargy may suggest a serious underlying cause	B2
Environmental context is important when assessing lethargy. Children who are lethargic in situations when they would normally be active or playing are worrying.	Agreed
Neuro-psychiatric symptoms can also manifest with an underlying brain tumour	B1
These include new onset mood disturbance, withdrawal and disinhibition	B1
Lethargy is an unusual behavioural response of children to adverse life events. Children are more likely to become angry or upset.	Recognition of brain tumours as a potential cause of lethargy rather than aetiology of all lethargy focus of guideline therefore not included.
In a child presenting with any of these symptoms enquiry should be made into the other symptoms of a brain tumour	B3

3.2.11 Head circumference

STATEMENT FROM WORKSHOP GROUP	DELPHI QUESTIONNAIRE STATEMENT
A rapidly increasing head circumference could be a sign of underlying brain tumour	H1
Head circumference not very often plotted after birth and 6 week check	Agreed that this is true but should not be the case
A rapid increase would be one that crosses 2 centiles	H2
If baby has increasing head circumference but otherwise well with no other symptoms then monitoring 2 weekly would be appropriate	H3

All babies who have increasing head circumference need to be assessed for other signs and symptoms of brain tumour	H4
Need to ensure head circumference plotted correctly as often patients referred to general paediatrics however, no problem as head circumference was incorrectly measured/plotted.	Not included as HCP's responsibility to check this.
MRI should be done in all children with rapidly increasing head circumference	H5

The multidisciplinary workshop encompassed a wide range of professionals from primary, secondary and tertiary care as well as patient representatives. The discussion allowed the current guideline statements to be reviewed as well as new statements to be derived around head circumference. At the end of the workshop, the guideline development group reviewed the discussion points and devised 30 statements to send out to the Delphi panel.

3.3 Delphi process

3.3.1 Delphi process round one

Round one of the Delphi consensus process comprised of 30 statements describing the presenting features of childhood brain tumours, factors that could be used to discriminate brain tumours from other less serious conditions and possible referral pathways for children with brain tumours.

137 clinicians were invited to take part in the Delphi process. 62 panel members returned the round one questionnaire within the required time frame. Statements were taken as having reached consensus if 75% or more of the Delphi panel respondents rated the statement 7, 8 or 9. Statements were rejected if 25% or less of the Delphi panel rated the statements 7, 8 or 9. Ratings of N/C, blanks or two boxes checked in error were excluded from the analysis of that statement.

Twenty four of the 30 original statements reached consensus, none were rejected and the remaining 6 statements were modified or excluded based upon feedback.

3.3.2 Delphi process round two

The statements for the second round of the Delphi consensus process were derived from the feedback of the first round. Round two of the Delphi consensus process comprised of 4 statements describing the presenting features of childhood brain tumours, factors that could be used to discriminate brain tumours from other less serious conditions and possible referral pathways for children with brain tumours.

Round two was issued to the 62 participants returning round one. The round two Delphi questionnaire, shown below, asked the panel to rank their agreement with 4 statements. Three of the 4 statements reached consensus, the remaining 1 statement was modified based upon unanimous feedback.

The Delphi questionnaires, results and comments are shown in Appendices 8 and 9.

4 CONCLUSIONS FROM THE EVIDENCE REVIEW

This literature review confirms that the patterns of presentation of brain tumours in children remains unchanged since the previous review. It also reiterates the importance of patient age and tumour location in determining the sign and symptom clusters present at diagnosis.

The most common signs and symptoms (the top 3) are all either specific or non-specific symptoms relating to raised intracranial pressure. Other alerts to a possible CNS tumour identified include visual signs, seizures, motor weakness, abnormal gait and coordination, cranial nerve palsies, behavioural changes (including lethargy and irritability) and school difficulties, developmental delay, head tilt, increasing head circumference, diabetes insipidus and other endocrinopathies, and abnormal growth.

Recognition that specific combinations of signs and symptoms indicate a focal CNS lesion is crucial to the diagnosis of many CNS tumours. Unfortunately, in this review there was a paucity of data on supratentorial tumours, however, the remainder of the analysis has emphasised the same sign and symptom combinations relating to different tumour locations as reported previously (Figure 8) [2]. Knowledge of these will help focus the search for corroborative findings in children who present with a sign or symptom that is potentially suggestive of a CNS tumour. In many instances, the possibility that the signs or symptoms are the result of a CNS tumour will be (rightly) rapidly dismissed. However, consideration of this diagnosis in some cases could lead to identification of corroborative signs and esymptoms and the instigation of imaging. Even if an underlying tumour is unlikely, patients and their families or carers should be encouraged to return for re-assessment should signs or symptoms persist or progress, and the diagnosis should be reviewed on re-presentation.

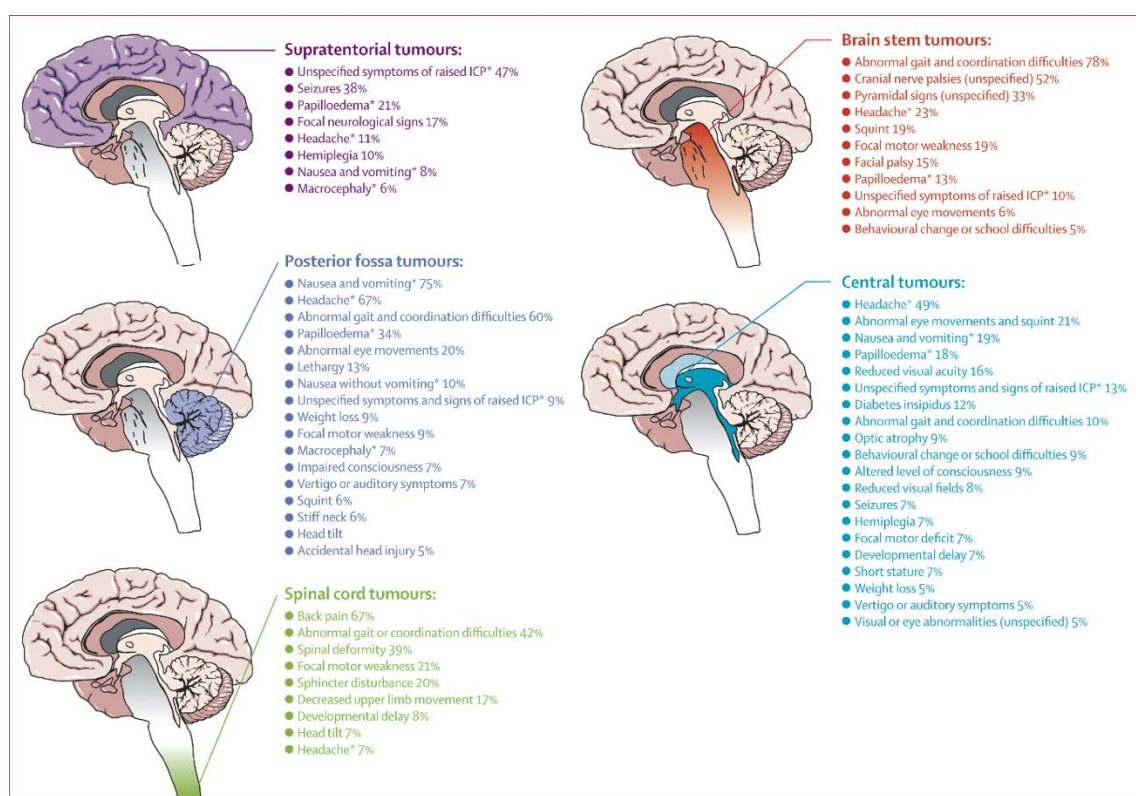


Figure 8: Symptom clusters by location [2]

Age is also a key factor in determining symptomatology. The review reiterates the previous review findings that increasing head circumference/macrocephaly is the most common symptom in the under 4s age group. This is a symptom that previously came under growth and development in the initial guideline, which we feel needs greater focus in the revised guidance.

A 2% threshold was chosen for reporting symptoms and signs in children with CNS tumours, as a practical compromise between the need to consider an underlying CNS tumour with a clinical feature not associated with this tumour type and those symptoms and signs that occur frequently in childhood CNS tumours. Nevertheless, the less common symptoms are often the ones associated with longer delays and so are important to highlight. Symptoms and signs that consistently occurred in less than 2% of patients, which could be associated with diagnostic difficulty, were torticollis/head tilt, abnormal growth and dysphagia.

Strengths and limitations

A systematic search strategy and standardised inclusion criteria was used, as recommended in the quality of reporting meta-analyses (QUOROM) statement, to identify studies for inclusion [152]. The high number of papers identified in the past 10 years shows the sustained interest in the mechanisms of diagnosis in this group of patients. The systematic approach has generated a cohort of patients doubling that of our previous review. The results reported here provide level 2 evidence for this cohort, which give greater value to the guideline statements.

Nevertheless there are some important limitations and potential sources of bias. The search strategy might not have identified all relevant papers and unpublished data were not sought. Papers included in the analysis reported signs and symptoms at diagnosis, therefore accuracy of these data depends on the history given by patients and their families/carers and the signs detected by the examining health-care practitioners. However, medical decisions will always be based on such histories and examination findings rather than the underlying full facts to which they relate. Furthermore, the assumption was made that if a sign or symptom was not described in a study, it did not occur in that population. The risk here is that this may under-represent the common symptoms and over-represent the rarer symptoms. In this case, we are interested in the pattern of presentation as opposed to ranking as we are looking for new signs and symptoms.

There was variation in the data detail between studies. Some studies were very detailed, recording individual signs and symptoms such as headache, vomiting, and papilloedema; whereas others used symptom complexes such as symptoms of raised intracranial pressure or cranial nerve palsies. This caused a coding difference which affected the pooled proportion and therefore makes it difficult to compare the two reviews in detail. Some signs and symptoms could have been combined to indicate the total proportion of children presenting with a specific symptom complex. However, since it could not be determined exactly how the data related, some inaccuracy and misrepresentation of data could result and thus the data was kept in their original form. Despite these problems, the analysis shows the variability of signs and symptoms and the general patterns with which they occur in childhood CNS tumours.

Summary

In summary, the meta-analysis shows both the heterogeneity of childhood CNS tumour presentation and the importance of tumour location and age in presentation. Assessment of any child who presents with signs and symptoms that could result from a CNS tumour should therefore include a thorough visual and motor system examination, assessment of growth (including head circumference in young children under 4 years), and pubertal status. Specific multiple signs and symptoms should alert the clinician to the possibility of a CNS tumour.

We have seen a positive response from both the public and healthcare professionals since the development of the initial guideline and subsequent launch of the HeadSmart: Be Brain Tumour Aware campaign. Increasing awareness of the varied and complex symptomatology that often occurs with CNS tumours has helped tumour diagnosis and reduce the extended symptom interval experienced by children across the UK [3]. Whilst this review supports the presenting patterns of symptomatology any new information, we recognise that increasing head circumference/ macrocephaly is the top presenting symptom in the under 4 age group and more robust guidance needs to exist for this symptom.

As for specificity, clinical assessment, referral pathways, imaging indications and acceptable waiting times, the Delphi consensus process provided consensus in the majority of statements devised as a result of the multi-disciplinary group (Appendix 8). A wide range of clinicians with different specialties have been involved, highlighting the range of professionals these symptoms will present to.

It is important to note that this method of recruiting the Delphi panel differed from the initial Delphi recruitment. The reasons are two-fold. The initial cohort study was not repeated as this was initially performed to gather baseline information on the total diagnostic interval across the UK which has since been collected annually through the Clinical Champions of the HeadSmart: Be Brain Tumour Aware campaign. Secondly, looking at the delays in diagnosis, the Guideline Development Group felt it was important to gain consensus from not just experts within the oncology and neurology field but also GPs, paediatricians and subspecialty consultants as they are the clinicians responsible for making the diagnosis. It is important to ensure the guideline was feasible from both a primary and secondary care perspective.

5 REVISED GUIDELINE

5.1 The diagnosis of brain tumours in children – an evidenced based guideline to assist healthcare professionals in the assessment of children presenting with symptoms and signs that may be due to a brain tumour

Statements in a **red box** advise on indications for imaging.

Statements in a **black box** advise on presentations frequently associated with misdiagnosis.

5.1.1a Best practice - consultation

Parents and their carers should be asked explicitly about their concerns in any consultation.

Strength of evidence

4

Recommendation form

Conditional

Consensus achieved 96% (original Delphi round 1)

Rationale

Parents / carers of children with brain tumours are frequently concerned that their child's symptoms may indicate a brain tumour for a significant period of time before the diagnosis is made. Parents / carers may be unwilling to express these concerns for fear of seeming over anxious or appearing to waste healthcare professionals' time. Explicitly asking parents / carers of their concerns enables them to be expressed improving communication between all parties. In some cases parental concern regarding a possible brain tumour may trigger professional concern and lead to appropriate investigation.

If a parent/carer expressed concerns about a brain tumour or symptoms attributable to a brain tumour this should be reviewed carefully. If a brain tumour is unlikely the reasons why should be explained by reference to the symptom card/decision support tool and appropriate safety netting advice given.

Strength of evidence 4

Recommendation form Conditional

Consensus achieved 80% (revision Delphi round 1)

Rationale

Parents / carers of children with brain tumours are frequently concerned that their child's symptoms may indicate a brain tumour for a significant period of time before the diagnosis is made. If on review a brain tumour seems unlikely it is important to explain why in order to maintain trust and communication with the patient and their parents / carers. The symptom card developed for parents and children is based on this guideline and is clear and concise way to safety net whilst acknowledging their concern.

If a child warrants a review, the timing of this review should comply with national diagnosis of all cancers (currently, diagnosis or all clear should be given to the patient within 4 weeks).

Strength of evidence 4

Recommendation form Conditional

Consensus achieved 83% (revision Delphi round 1)

Rationale

Symptom progression occurs with childhood brain tumours therefore early review is recommended to facilitate detection of any additional symptoms or signs which may make the diagnosis more likely. The Independent Cancer Taskforce published a strategy for the NHS in July 2015 which aims for all patients with suspected cancer to have a diagnosis or the all clear within 4 weeks by 2010 and the Guideline Development Group felt that this target should be reflected in this guideline [157].

If the patient, parent / carer and healthcare professional are not fluent in a common language an interpreter must be used for the consultation (www.languageline.co.uk).

Strength of evidence 4

Recommendation form Strong

Consensus achieved 94% (original Delphi round 1)

Rationale

The Guideline Development Group, Delphi workshop and Delphi panel could all identify individual cases where non-English first language was associated with diagnostic delay. It is essential to take a thorough history when assessing a child who may have a brain tumour; this

is not possible if the patient, parent / carer and healthcare professional are not fluent in a common language.

Low parental educational level, social deprivation and lack of familiarity with the UK healthcare system may be associated with diagnostic delay. Care must be taken for appropriate safety netting and multi-disciplinary approach in these families.

Strength of evidence 4
Recommendation from Conditional
Consensus achieved 86% (revision Delphi round 1)

Rationale

There is no published evidence linking low parental education, social deprivation and lack of familiarity with the UK healthcare system with diagnostic delay in paediatric brain tumours, however the research team and many members of the first Delphi panel were aware of individual cases in which these factors may have contributed to a prolonged symptom interval. The revision multi-disciplinary workshop group highlighted that these children may not necessarily need quicker referral but actually would benefit with thorough safety netting and health visitor support to ensure any new symptoms were not missed.

5.1.1b Best practice – referral

A primary healthcare professional who has a high index of suspicion regarding a possible brain tumour should discuss their concerns with a secondary health care professional the same day.

Strength of evidence 4
Recommendation form Strong
Consensus achieved 80% (original Delphi round 1)

Rationale

Children who have a brain tumour may deteriorate quickly and therefore if there is a high possibility that they may have a brain tumour they should be assessed and arrangements made for CNS imaging as quickly as possible.

A child referred from primary care in which the differential diagnosis includes a possible space-occupying lesion should be seen in a rapid-access clinic or similar service (i.e. within 2 weeks)

Strength of evidence 4
Recommendation form Strong
Consensus achieved 79% (revision Delphi round 1)

Rationale

A prolonged symptom interval with brain tumours occurs in part due delay between initial referral from primary care and assessment in secondary care [158, 159, 160]. The Department of Health has advised that a patient presenting with symptoms that are potentially indicative of a malignancy should be assessed by a healthcare professional with expertise in that area within 2 weeks [161]. The original Delphi panel agreed that this recommendation was appropriate for children who may have a brain tumour.

5.1.1c Best practice – imaging

A child in whom CNS imaging is required to exclude a brain tumour (potential diagnosis but low index of suspicion) should be imaged and reported within 4 weeks to meet Department of health recommendations.

Strength of evidence 4
Recommendation form Strong
Consensus achieved 83% (revision Delphi round 1)

Rationale

There is frequently reluctance amongst healthcare professionals to undertake CNS imaging of children who may have a brain tumour until clinical signs become florid. This results in a prolonged symptom interval and children who may be extremely unwell by diagnosis. The NICE guideline on diagnosis and management of epilepsy in primary and secondary care advises that children who present with a focal onset of seizures should undergo CNS imaging within 4 weeks [162]. As imaging in this case is required to exclude a CNS space occupying lesion (including brain tumours) it seemed appropriate to advise a similar waiting time to imaging for children who present with other symptoms and signs that may be due to a brain tumour. Given the 2015 Independent Cancer Taskforce report states that a diagnosis or all clear should be given within 4 weeks, we have amended this statement to include that a result should also be available within 4 weeks [157].

MRI is the imaging modality of choice for a child who may have a brain tumour.

Strength of evidence 2++
Recommendation form Strong
Consensus achieved 85% (original Delphi round 1)

Rationale

As advised by the Royal College of Radiologists[160].

If MRI is not available a contrast enhanced CT should be performed.

Strength of evidence 2++
Recommendation form Strong
Consensus achieved 92% (original Delphi round 1)

Rationale

As advised by the Royal College of Radiologists[160].

Imaging results should be interpreted by a professional with expertise and training in central nervous system MR and CT imaging in children.

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 93% (original Delphi round 1)

Rationale

Normal and abnormal neuro-imaging findings can vary significantly between children and adults. In order to reduce the risk of misdiagnosis the Delphi panel agreed that central nervous system imaging in children should be interpreted by a healthcare professional with expertise in this area.

The need to sedate or anaesthetise a child for imaging should not delay diagnosis and should be compliant with Department of Health guidance.

Strength of evidence 4
Recommendation form Strong
Consensus achieved 93% (revision Delphi round 1)

Rationale

Young children (under 5 years) are frequently unable to keep still enough to allow adequate CNS imaging. In this situation they require sedation or a general anaesthetic for imaging. The Delphi panel felt that the diagnosis of brain tumours in young children should not be significantly delayed due to the requirement for sedation or a general anaesthetic. The revision workshop group felt that this should be changed to keep in line with the 2015 Independent Cancer Taskforce strategy [157].

5.1.2 Predisposing factors

Some predisposing factors (personal or family history of brain tumour, leukaemia, sarcoma and early onset breast cancer; prior therapeutic CNS radiation; NF1/2; tuberous sclerosis) are associated with an increased risk of childhood brain tumours. Patients/parents should be specifically asked about these factors in consultation as their presence may lower the threshold for referral and investigation.

Strength of evidence 2++
Recommendation form Strong
Consensus achieved 90% (revision Delphi round 1)

Rationale

The above are all associated with an increased risk of childhood brain tumours and therefore their presence should alert the clinician to this possibility and may lower their threshold for referral and investigation[163]. The majority of the association between brain tumours, leukaemia, sarcoma and early onset breast cancer is due to inherited abnormalities in the P53 tumour suppressor gene (Li Fraumeni syndrome). There are associations between brain tumours and colorectal polyposis and colorectal cancer (Turcot's syndrome) and with basal-cell nevus syndrome (Gorlin's syndrome). Having a parent or sibling with a brain tumour is associated with an increased risk however this is probably due to the above genetic associations.

5.1.3 Presentation and assessment of a child with a potential brain tumour

The following symptoms and signs are all associated with childhood brain tumours. Their presence should alert the clinician to this possibility.

5.1.3a Headache

Headache

Strength of evidence 2++
Recommendation form Strong
Consensus achieved 91% (original Delphi round 1)

Rationale

Depending on patient age and tumour location between 10% and 67% of children reported in the initial meta-analysis had a headache at diagnosis. In the cohort study 40% of children at

symptom onset and 58% by diagnosis had a headache. In the new meta-analysis the pooled proportion of children with a headache was 23% [4-151].

Nausea and / or vomiting

Strength of evidence 2++

Recommendation form Strong

Consensus achieved 91% (original Delphi round 1)

Rationale

Between 10% and 67% of children reported in the initial meta-analysis had experienced nausea and / or vomiting by diagnosis [2]. In the cohort study 40% of children at symptom onset and 58% by diagnosis experienced nausea or vomiting [1]. In the new meta-analysis, the pooled proportion of children with nausea and/or vomiting was 13%[4-151].

Increasing head circumference (crossing centiles)

Strength of evidence 2++

Recommendation form Strong

Rationale

In the new meta-analysis, the pooled proportion of children presenting with an increasing head circumference or macrocephaly was 3% [4-151] but in the under 4 age group, it was the most common presenting symptom [16, 21, 25, 27, 38, 47, 50, 51, 75, 80, 85, 113, 122, 138, 139, 148, 151]. The Guideline Development Group felt it was important to highlight this more prominently in the guideline, as it had previously been included under growth and development. The revision multidisciplinary workshop group agreed. Statements regarding head circumference were included within the revision Delphi consensus process.

Visual symptoms and signs

Reduced visual acuity

Reduced visual fields

Abnormal eye movements

Abnormal fundoscopy

Strength of evidence 2++

Recommendation form Strong

Consensus achieved 91% (original Delphi round 1)

Rationale

Between 10% and 41% of children reported in the initial meta-analysis had experienced a visual symptom or sign. Reduced visual acuity occurred in up to 41% of patients, reduced visual fields in up to 5%, abnormal eye movements in up to 20% and abnormal fundoscopy in up to 34% [2]. In the cohort study 17% of children at symptom onset and 70% by diagnosis had a visual system abnormality [1]. In the new meta-analysis, the pooled proportion of children with visual symptoms (NOS) was 10%, papilloedema was 3% and abnormal eye movements was 2% [4-151].

Motor symptoms and signs

Abnormal gait

Abnormal co-ordination

Focal motor abnormalities

Strength of evidence 2++

Recommendation form *Strong*
Consensus achieved *91% (original Delphi round 1)*
 Rationale

Between 7% and 78% of children reported in the initial meta-analysis had experienced a motor system abnormality. Abnormal gait and co-ordination occurred in up to 78% of patients and focal motor abnormalities in up to 19%. In the cohort study 22% of children at symptom onset and 67% by diagnosis had a motor system abnormality. In the new meta-analysis, the pooled proportion of children presenting with motor weakness was 5%, cranial nerve palsies was 5%, ataxia was 4%, and gait/co-ordination difficulties was 3%.

Growth and endocrine abnormalities

Growth failure

Delayed, arrested or precocious puberty

Galactorrhoea

Primary or secondary amenorrhoea

Strength of evidence *2++*
Recommendation form *Strong*
Consensus achieved *91% (original Delphi round 1)*
 Rationale

Between 5% and 14% of children reported in the initial meta-analysis experienced growth or developmental abnormalities. Growth failure occurred in up to 14% and pubertal abnormalities in up to 8%[2]. In the cohort study endocrine and growth abnormalities occurred in 7% of children at symptom onset and 25% by diagnosis [1]. In the new meta-analysis, the pooled proportion of children with a growth problem was 1%, galactorrhoea was 1% and menstrual irregularities was 1% [4-151]. HeadSmart cohort data has shown that the subtypes of brain tumours with the longest total diagnostic intervals are midline supratentorial tumours such as craniopharyngiomas. These tumours commonly present with growth and endocrine symptoms. The guideline development group and revision multi-disciplinary workshop group felt that the endocrine symptoms needed to be highlighted in order to make healthcare professionals aware of brain tumour as a possibility.

Behavioural change

New onset mood disturbance

Lethargy

Withdrawal

Disinhibition

Strength of evidence *2++*
Recommendation form *Strong*
Consensus achieved *91% (original Delphi round 1)*
 Rationale

Between 5% and 21% of children reported in the initial meta-analysis experienced a behavioural change[2]. In the cohort study a behavioural change occurred in 3% of children at symptom onset and 40% by diagnosis [1]. In the new meta-analysis, the pooled proportion of children or young people with a behavioural or educational change was 2% [4-151]. The symptoms highlighted in the systematic review included mood disturbance, withdrawal and disinhibition as well as lethargy. The Guideline Development Group felt it was important to include these

symptoms as the research group could recall a number of patients with a brain tumour who had initially been diagnosed with a psychiatric illness.

Diabetes insipidus

Strength of evidence 2++

Recommendation form Strong

Consensus achieved 84% (original Delphi round 3)

Rationale

Up to 12% of children in the initial meta-analysis experienced diabetes insipidus [2]. One child in the cohort study presented with diabetes insipidus [1]. In the new meta-analysis, the pooled proportion of patients with diabetes insipidus was 1% [4-151].

Symptoms and signs in childhood brain tumours may occur singularly or in combination.

Strength of evidence 2+

Recommendation form Strong

Rationale

In the cohort study children had a median of one symptom or sign (range 1-8) at symptom onset. This had increased to a median of six (range 1-16) by diagnosis [1].

5.1.3b History

Take a detailed history.

Enquire specifically about associated symptoms and predisposing factors

Strength of evidence 4

Recommendation form Strong

Consensus achieved 89% (original Delphi round 1)

Rationale

Childhood brain tumours frequently present with symptoms that may occur with other more common childhood illnesses. Taking a detailed history including specifically enquiring about any other symptoms and predisposing factors facilitates identifying those children who may have tumours and need imaging from the majority who don't.

5.1.3c Assessment

Assess: Visual system

Motor system

Height and weight

Pubertal status

Head circumference if under 2 years

Strength of evidence 2+

Recommendation form Strong

Consensus achieved 89% (original Delphi round 1)

Rationale

By diagnosis 95% of children in the cohort study presented with one or more of the following: headache, nausea and vomiting, visual system abnormality and / or motor system abnormality. In children presenting with a symptom that may be due to a brain tumour, the detection of an abnormality in their growth, pubertal status or motor and visual systems increases the likelihood that the child does have an intracranial lesion. Thus, detailed assessment of these

areas will facilitate identification of children who may have a brain tumour from the majority who do not.

The initial symptoms of a brain tumour frequently mimic those that occur with many common childhood conditions

<i>Strength of evidence</i>	2+
<i>Recommendation form</i>	Strong
<i>Consensus achieved</i>	94% (original Delphi round 1)

Rationale

One of the reasons that it can be difficult for health care professionals to identify children with a brain tumour early on in their symptom interval is that brain tumours may present with symptoms that occur with many other less serious childhood conditions. In the cohort study 40% of children initially presented with a headache, 28% with nausea and vomiting, 17% with a cranial nerve palsy, 10% seizures and 3% a behavioural change. Highlighting this presentation pattern will encourage clinicians to consider a brain tumour in the differential diagnosis of children presenting with the above symptoms.

Symptoms frequently fluctuate in severity – resolution and then recurrence does not exclude a brain tumour

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	Conditional
<i>Consensus achieved</i>	77% (original Delphi round 1 – fluctuation in symptoms) 83% (original Delphi round 1 – resolution and then recurrence)

Rationale

Symptom fluctuation is common in children with brain tumours however clinicians may mistakenly assume that symptom fluctuation rules out a brain tumour. There is no published evidence to support this however there is significant professional experience of this phenomenon, demonstrated by the consensus agreement level achieved in the Delphi process.

Presentation depends upon the age of the child

<i>Strength of evidence</i>	2++
<i>Recommendation form</i>	Strong
<i>Consensus achieved</i>	91% (original Delphi round 1)

Rationale

The meta-analysis and cohort study clearly demonstrate that young children (3 years and under) with brain tumours present very differently to older children.

A normal neurological examination does not exclude a brain tumour

<i>Strength of evidence</i>	2+
<i>Recommendation form</i>	Strong
<i>Consensus achieved</i>	89% (original Delphi round 1)

Rationale

Not all children with a brain tumour will develop a neurological abnormality and clinicians need to be aware that a normal neurological examination does not exclude a brain tumour. In the cohort study 48 children at symptom onset had a normal neurological examination and at diagnosis 2 children had no neurological signs and one child had hearing loss alone.

It is important to note that as the symptoms are non-specific, some children may be referred to sub-specialty doctors. A detailed history and assessment is required in these children if the cause of the symptoms is not clear.

Recommendation grade *Good practice points*

Rationale

The workshop group agreed that as the symptoms are non-specific, some of these children will be referred to sub-specialty paediatricians. Experts in the group could all recall cases where a child experienced a significant delay in diagnosis due to multiple referrals to various teams for example, to a respiratory physician for recurrent chest infections which was secondary to recurrent aspiration caused by a brain stem tumour. It was agreed that this would be highlighted in the guideline but did not need to go to Delphi consensus. Figure 2 is an awareness poster showing the different systems in which the brain tumour symptoms present.

5.1.4 Signs and symptoms of a child with a potential brain tumour

5.1.4a Headache

Headache is a common symptom and is very rarely, in isolation, due to a brain tumour.

Strength of evidence *2+*

Recommendation form *Conditional*

Consensus achieved *84% (revision Delphi round 1)*

Rationale

Depending on patient age and tumour location between 10% and 67% of children reported in the initial meta-analysis had a headache at diagnosis. In the cohort study 40% of children at symptom onset and 58% by diagnosis had a headache. In the new meta-analysis, a pooled proportion of 32% presented with a headache.

Headache is an extremely common complaint in school age children and usually occurs in association with benign, self-limiting illness or in the context of a headache syndrome (migraine or tension headache). The cohort study showed it was very rare to have a brain tumour with only headache as a symptom. It is therefore important to provide guidance as to the characteristics of a headache that increase the likelihood that it is due to an underlying brain tumour. The multidisciplinary workshop highlighted the new NICE guidance regarding headaches in children over the age of 12 which highlights red flag symptoms and this should be referred to for children in this age group if no other symptoms suggestive of a brain tumour is present [164].

Any child presenting with a headache should be assessed carefully for the other symptoms of a brain tumour, as listed in the guideline.

Strength of evidence *2++*

Recommendation form *Strong*

Consensus achieved *97% (revision Delphi round 1)*

Rationale

The cohort study showed that a headache very rarely occurs in isolation due to a brain tumour. The Delphi panel agreed that all children with a headache need to be specifically assessed for the other symptoms of a brain tumour in order to ensure the diagnosis is not missed.

Brain tumour headaches can occur at any time of the day or night

<i>Strength of evidence</i>	2+
<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	84% (original Delphi round 1)

Rationale

The headache that occurs with raised intracranial pressure classically occurs first thing in the morning after a prolonged period of sleep[165,166]. In children this pattern is less common and whilst a headache occurring first thing in the morning is suggestive of raised intracranial pressure, occurrence of a headache at any other time of the day does not exclude raised intracranial pressure[1].

A child with a headache without a clear cause requires careful review, the timing of which needs to be mindful of the differential diagnoses.

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	81% (revision Delphi round 1)

Rationale

The revision workshop group agreed that whilst headaches were a common presentation, review needed to be mindful of the differential diagnoses. If a brain tumour is in the differential diagnosis then the timing of review needs to be in line with the 2015 Independent Cancer Taskforce report [157]. We have made reference to the NICE guideline for headaches in over 12s which covers all differential diagnoses of headaches in this age group [164].

Children aged younger than 4 years are frequently unable to describe headache; their behaviour e.g. withdrawal, holding head may indicate a headache.

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	98% (original Delphi round 1)

Rationale

The initial meta-analysis and cohort study clearly demonstrate that young children (3 years and under) with brain tumours present very differently to older children and that headache is much less common complaint in this age group [2]. The incidence of raised intracranial pressure is similar in both age groups and therefore presumably younger children do experience headache but due to their development level and language ability are unable to vocalise this symptom; their behaviour, however, may suggest that they are in pain. It is important that health professionals, particularly those who infrequently assess young children, are aware that the absence of headache in a young child does not exclude a brain tumour and that enquiry into relatively subtle behavioural changes may suggest that young children are in pain.

In a child with a known migraine or tension headache a change in the nature of the headache requires reassessment and review of the diagnosis.

<i>Strength of evidence</i>	3
<i>Recommendation form</i>	<i>Strong</i>
<i>Consensus achieved</i>	86% (original Delphi round 2)

Rationale

Headache in childhood is rarely due to a brain tumour; other common causes include self-limiting infections and headache syndromes such as migraine or tension headache. The presence of a headache syndrome does not prevent the development of a brain tumour and

therefore any change in the nature of headache in these situations requires reassessment and review of the diagnosis[167].

Delayed diagnosis has been associated with:

- **Failure to reassess a child with migraine or tension headache when the headache character changes.**

Strength of evidence 3

Recommendation form Conditional

Rationale

The guideline development team felt that it was particularly important to highlight presenting symptoms and signs which, whilst not necessarily common presentations of childhood brain tumours, were, in their experience, particularly associated with a prolonged symptom interval and diagnostic difficulty. In order to make these areas easy to identify in the guideline they have been headed with the caption “Delayed diagnosis has been associated with:”. The above statement leads on from the proceeding statement “In a child with a known migraine or tension headache a change in the nature of the headache requires reassessment and review of the diagnosis” and was therefore not sent to the Delphi group.

CNS imaging required for:

Persistent headaches that wake a child from sleep

Strength of evidence 4

Recommendation form Strong

Consensus achieved 88% (original Delphi round 1)

Persistent headaches that occur on waking

Strength of evidence 4

Recommendation form Strong

Consensus achieved 88% (original Delphi round 1)

A persistent headache occurring at any time in a child younger than 4 years

Strength of evidence 4

Recommendation form Strong

Consensus achieved 89% (original Delphi round 1)

Confusion or disorientation occurring with a headache

Strength of evidence 4

Recommendation form Strong

Consensus achieved 92% (original Delphi round 1)

Persistent headache with one or more other symptoms/signs suggestive of a brain tumour.

Strength of evidence 4

Recommendation form Conditional

Rationale

For the rationale behind the maximum waiting time to imaging and the definition of a persistent headache see statements above.

There are certain characteristics of headache that increase the likelihood that the headache is due to a brain tumour and thus their presence should lower the threshold for imaging. Headaches due to raised intracranial pressure are characteristically worse after a prolonged period of lying down[165, 166] and thus any persistent headache that wakes a child from sleep

or occurs on waking is suggestive of an intracranial space occupying lesion. Headache is an unusual complaint in young children and complaint of persistent headache in this age is very unusual. Confusion or disorientation with a headache increases the likelihood of an underlying CNS lesion. The Delphi panel agreed that these following headache characteristics increase the likelihood of an underlying brain tumour to such an extent that CNS imaging is required even in the absence of other symptoms and signs. Regarding the final statement, the Guideline Development Group and revision workshop group felt that if any 2 or more symptoms suggestive of a brain tumour was present, then an MRI scan was warranted.

5.1.4b Nausea and vomiting

Early specialist referral for consideration of underlying causes including CNS causes is required for a child with persistent nausea and / or vomiting. (Nausea and / or vomiting that lasts for more than two weeks should be regarded as persistent)

Strength of evidence 2++

Recommendation form Conditional

Consensus achieved 85% (original Delphi round 2)

Rationale

Depending on patient age and tumour location between 8% and 75% of children reported in the meta-analysis had nausea and / or vomiting at diagnosis. In the cohort study 28% of children at symptom onset and 63% by diagnosis had nausea and / or vomiting. In the new systematic review a pooled proportion of 13% of children and young people presented with nausea/vomiting.

Nausea and vomiting are extremely common complaints in children and usually occur in association with benign, self-limiting illnesses. It is therefore important to provide guidance as to the characteristics of nausea and vomiting that increase the likelihood that they are due to an underlying brain tumour. As there is little published evidence in this area professional expertise via the Delphi panel was used to identify factors predictive of a brain tumour. The panel concluded that if nausea and / or vomiting were continuous or recurrent for more than 2 weeks then the likelihood of an underlying brain tumour is increased and this should be considered in the differential diagnosis.

Young children under the age of 2 who may not be able to communicate other symptoms of raised intracranial pressure should have their head circumference measured, plotted and compared with previous measurements.

Strength of evidence 4

Recommendation form Strong

Consensus achieved 79% (revision Delphi round 1)

The Delphi panel agreed that in young babies with persistent vomiting, measuring and monitoring the head circumference would enable assessment of the possibility of raised intracranial pressure as a cause. The guideline development group felt that this needed to be highlighted as failure to consider a central cause of persistent nausea and vomiting, particularly in babies, has been associated with a prolonged symptom interval and diagnostic difficulties.

Delayed diagnosis has been associated with:

- **Attributing persistent nausea and vomiting to an infective cause (in the absence of corroborative findings e.g. contact with similar illness, pyrexia, diarrhoea).**

<i>Strength of evidence</i>	3
<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	79% (original Delphi round 1)

The Delphi panel agreed that in the absence of corroborative findings persistent nausea and vomiting should not be attributed to an infective course. The guideline development group felt that this presentation needed to be highlighted as failure to consider a central cause of persistent nausea and vomiting, particularly in young children, has been associated with a prolonged symptom interval and diagnostic difficulties.

CNS imaging is required for persistent vomiting on awakening (either in the morning or from a day time sleep). N.B. exclude pregnancy where appropriate.

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	<i>Strong</i>
<i>Consensus achieved</i>	88% (original Delphi round 1)

Rationale

For the rationale behind the maximum waiting time to imaging and the definition of persistent vomiting see statements above.

Vomiting due to raised intracranial pressure is characteristically worse after a prolonged period of lying down[165, 166] and thus vomiting that persistently occurs on waking is more likely to be associated with an intracranial lesion than vomiting occurring at other times. The Delphi panel agreed that this increased the likelihood of a brain tumour to such an extent that CNS imaging is required even in the absence of other symptoms and signs. Early pregnancy is obviously a common cause of vomiting on waking and it is important to exclude (a concealed) pregnancy where appropriate.

Persistent nausea and/or vomiting with 1 or more other symptoms/signs associated with a brain tumour (i.e. headache, visual symptoms, increasing head circumference, motor symptoms, growth and development abnormalities, behavioural change) require CNS imaging.

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	<i>Strong</i>
<i>Consensus achieved</i>	91% (revision Delphi round 1)

Rationale

The Guideline Development Group felt that if there were 2 or more symptoms present, CNS imaging was indicated to rule out a space occupying lesion. The Delphi panel were in agreement with this and an editorial decision was made to make this recommendation across the guideline.

5.1.4c Head Circumference

A rapidly increasing head circumference (crossing centiles) can be a sign of an underlying brain tumour and requires referral to secondary care.

<i>Strength of evidence</i>	2++
<i>Recommendation form</i>	<i>Strong</i>
<i>Consensus achieved</i>	93% (revision Delphi round 1)

Rationale

Increasing head circumference/ macrocephaly was the most common presenting symptom in under 5s highlighted in the new systematic review, therefore the Guideline Development Team felt it was necessary to add a section to the current guideline to advise clinicians on assessment and referral of this symptom.

In all babies with an increasing head circumference (crossing centiles), careful assessment of other symptoms of signs associated with a brain tumour should be undertaken.

Strength of evidence 4

Recommendation form Conditional

Consensus achieved 88% (revision Delphi round 1)

Rationale

The workshop group felt that all babies with increasing head circumference should be asked or assessed for the other signs and symptoms of a brain tumour in order to expedite imaging and diagnosis. The revision Delphi panel agreed with this.

In babies in whom a HC circumference is crossing centiles and a brain tumour is suspected an MRI is the imaging modality of choice.

Strength of evidence 2++

Recommendation form Strong

Consensus 71 % (revision Delphi round 2)

Rationale

MRI is the imaging modality of choice if suspecting a brain tumour (ref). The original statement sent to Delphi panel included “within 4 weeks”. This statement did not reach consensus and all comments noted that 4 weeks would be too long to wait for a scan for a child with an increasing head circumference. This was taken back to the Guideline Development Group who felt that removing the statement “within 4 weeks” would be sufficient due to the strong opinion and this did not need to go back out to another round of Delphi.

Delayed diagnosis has been associated with:

- **Failure to measure head circumference in a baby or young child with persistent vomiting.**

Strength of evidence 4

Recommendation form Conditional

Rationale

The Guideline development team felt that this point should be highlighted as head circumference is often not measured in under 2s with vomiting. In order to make these areas easy to identify in the guideline they have been headed with the caption “Delayed diagnosis has been associated with:”. The Delphi group agreed that increasing head circumference can be a sign of a brain tumour and that it should be measured in babies with persistent vomiting so this statement was therefore not sent to the Delphi group.

CNS imaging is required for: An increasing head circumference (crossing centiles) with 1 or more other symptoms/signs associated with a brain tumour (i.e. headache, nausea/vomiting, visual symptoms, motor symptoms, endocrine or growth symptoms, behavioural change).

Strength of evidence 4

Recommendation form Strong

Rationale

The Guideline Development Group and multidisciplinary workshop agreed that 2 persistent symptoms warranted an MRI scan. The Delphi group reached consensus on the statement regarding nausea/vomiting plus another symptom and this was editorially agreed to be implemented across the guideline for all symptoms.

5.1.4d Visual symptoms and signs

Consider a brain tumour in any child presenting with a persisting visual abnormality. (Any visual abnormality lasting longer than 2 weeks should be regarded as persistent)

Strength of evidence 2++

Recommendation form Strong

Consensus achieved 91% (original Delphi round 1)

Rationale

Depending on patient age and tumour location between 7% and 41% of children reported in the meta-analysis had a visual system abnormality at diagnosis [1]. In the cohort study 17% of children at symptom onset and 70% by diagnosis had a visual system abnormality [1]. The Delphi panel agreed that if a visual abnormality persisted for more than two weeks then the likelihood of an underlying brain tumour is increased and this should be considered in the differential diagnosis.

Parental / carer concern alone (including nursery staff) regarding a baby or young child's vision should be taken seriously and a referral for visual assessment should be made.

Consensus achieved 97% (revision round 1)

Rationale

The revision workshop group agreed that they had all come across cases where persistent parental or carer concern despite health professional reassurance had led to significant diagnoses. The Delphi panel agreed that any child with parental concern regarding their vision should have a formal visual assessment arranged.

Visual assessment must include assessment of:

Pupil responses

Strength of evidence 2+

Recommendation form Strong

Consensus achieved 91% (original round 1)

Rationale

Brain tumours may cause unequal pupil responses [134]. In the cohort study 1% of children at symptom onset and 4% by diagnosis had unequal pupils. It is therefore important to assess pupil responses in children who may have a brain tumour.

Acuity

Strength of evidence 2++

Recommendation form Strong

Consensus achieved 91% (original Delphi round 1)

Rationale

41% of children with neurofibromatosis and a brain tumour and 16% of children with a central tumour (no neurofibromatosis) in the meta-analysis had a reduced visual acuity at diagnosis [2].

In the cohort study 4% of children at symptom onset and 14% at diagnosis had reduced visual acuity [1]. It is therefore important to assess visual acuity in children who may have a CNS tumour.

Visual fields in school age children

Strength of evidence 2++
Recommendation form Strong
Consensus achieved 91% (original Delphi round 1)

Rationale

5% of children with neurofibromatosis and a brain tumour and 8% of children with a central tumour (no neurofibromatosis) in the meta-analysis had reduced visual fields at diagnosis [2]. In the cohort study 1% of children at symptom onset and 8% at diagnosis had reduced visual fields [1]. It is therefore important to assess visual fields in children who may have a CNS tumour however due to the co-operation required this is only technically possible in school age children.

Eye movements

Strength of evidence 2++
Recommendation form Strong
Consensus achieved 91% (original Delphi round 1)

Rationale

Depending upon tumour location between 6% and 21% of children in the meta-analysis had abnormal eye movements (squint, nystagmus, Parinaud's syndrome) at diagnosis [2]. In the cohort study 3% of children at symptom onset and 21% at diagnosis had abnormal eye movements [1]. It is therefore important to assess eye movements in children who may have a CNS tumour.

Optic disc appearance

Strength of evidence 2++
Recommendation form Strong
Consensus achieved 91% (original Delphi round 1)

Rationale

Depending upon tumour location between 10% and 34% of children in the meta-analysis had papilloedema at diagnosis [2]. 9% of children with a central tumour and 15% of children with neurofibromatosis had optic atrophy at diagnosis [2]. In the cohort study 1% of children at symptom onset and 6% at diagnosis had optic atrophy and 34% had papilloedema at diagnosis [1]. It is therefore important to assess optic disc appearance in children who may have a CNS tumour.

If the assessing healthcare professional is unable to perform a complete visual assessment the child should be referred for assessment.

Strength of evidence 4
Recommendation form Strong
Consensus achieved 85% (original Delphi round 1)

Rationale

It can be difficult to assess the visual system in children and health professionals with expertise in other areas may not feel that they can adequately assess a child's visual system. Because of the frequency of visual system abnormalities in childhood brain tumours the Delphi panel

concluded that in this situation referral for assessment by an optician or ophthalmologist is appropriate.

Children referred for visual assessment with symptoms or signs suggestive of a brain tumour should be seen in a rapid access clinic or similar service (i.e. within 2 weeks).

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 85% (original Delphi round 1)

Rationale

A prolonged symptom interval with brain tumours occurs in part due delay between initial referral and assessment [168, 169]. The Department of Health has advised that a patient presenting with symptoms that are potentially indicative of a malignancy should be assessed by a healthcare professional with expertise in that area within 2 weeks [161]. The Delphi panel agreed that this recommendation was appropriate for children who may have a brain tumour. An Editorial decision was made by the Guideline Development Group to change this to rapid access/similar service to keep in line with the referral statement agreed at Delphi.

Community optometry should refer any child with abnormal eye findings suggestive of a possible brain tumour directly to secondary care.

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 83% (original Delphi round 1)

Rationale

Currently, if a community optometrist recommends a child for ophthalmology assessment the referral pathway usually requires the patients GP to refer the child to ophthalmology. This referral pathway can be time consuming and the significance of the eye findings may not be fully understood by the referring healthcare professional. Community optometrists have expertise in visual system assessment and therefore should be able to refer directly to secondary care when this is indicated.

Consideration should be given to the appropriate place of assessment. If appropriate community optometry expertise is not available, pre-school and uncooperative children should be assessed by the hospital eye service.

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 81% (original Delphi round 1)

Rationale

Assessment of the visual system in young or uncooperative children can be challenging and requires expertise. Community optometry experience in assessing young children varies and if appropriate expertise is not available in the community children should be referred to hospital (paediatric) ophthalmology departments for assessment.

A child with a new onset non-paralytic (concomitant) squint should have early ophthalmological assessment for consideration of underlying causes (including CNS causes).

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 92% (original Delphi round 2)

Rationale

Non-paralytic squints may be due to a brain tumour (e.g. optic atrophy with optic pathway gliomas), however other causes (e.g. congenital, hypermetropia, cataract, retinal disease) are more common [170, 171]. The Delphi panel therefore concluded that whilst children with a concomitant squint required early assessment this should be in the first instance by an ophthalmologist who could then determine the need for CNS imaging. (See also non-concomitant squint below)

Delayed diagnosis has been associated with:

- **Failure to fully assess vision in a young or uncooperative child**
- **Failure of communication between community optometry and primary and secondary care**

Strength of evidence 4

Recommendation form Conditional

Rationale

Whilst uncommon, the guideline development group wanted to highlight the importance of adequately assessing vision in young or uncooperative children and of ensuring thorough communication between community optometry and primary and secondary care as difficulties in both these areas have been associated with a prolonged symptom interval and difficult diagnosis.

CNS imaging is required for:

Papilloedema

Strength of evidence 4

Recommendation form Strong

Consensus achieved 97% (original Delphi round 1)

Rationale

Papilloedema is due to raised intracranial pressure, causes of which include a brain tumour. See above for frequencies of papilloedema in the meta-analysis and cohort study. The presence of papilloedema increases the likelihood of an underlying CNS lesion, including a brain tumour, to such an extent that the Delphi panel agreed that CNS imaging is required even in the absence of other symptoms and signs.

Optic atrophy

Strength of evidence 4

Recommendation form Conditional

Consensus achieved 85% (original Delphi round 1)

Rationale

Optic atrophy may be due to a brain tumour involving the optic pathway. See above for frequencies of optic atrophy in the meta-analysis and cohort study. The Delphi panel agreed that the presence of optic atrophy increased the likelihood of an underlying CNS lesion, including a brain tumour, to such an extent that CNS imaging is required even in the absence of other symptoms and signs.

New onset nystagmus

Strength of evidence 4

<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	<i>91% (original Delphi round 1)</i>

Rationale

Whilst nystagmus has causes other than CNS lesions [172], new-onset nystagmus increases the likelihood of an underlying CNS lesion, including a brain tumour, to such an extent that the Delphi panel agreed that CNS imaging is required even in the absence of other symptoms and signs. See above for frequencies of nystagmus in the meta-analysis and cohort study.

Reduction in visual acuity not attributable to an ocular cause

<i>Strength of evidence</i>	<i>4</i>
<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	<i>81% (original Delphi round 1)</i>

Rationale

A refractive error is the commonest cause of a reduction in visual acuity in children however in the absence of this it is important to exclude other causes, particularly those due to a CNS lesion. The Delphi panel agreed that even in the absence of other symptoms and signs a reduction in visual acuity in the absence of a refractive error increased the likelihood of an underlying CNS tumour to such an extent that CNS imaging is required. See above for frequencies of reduced visual acuity in the meta-analysis and cohort study.

Visual field reduction not attributable to an ocular cause

<i>Strength of evidence</i>	<i>4</i>
<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	<i>83% (original Delphi round 1)</i>

Rationale

Visual field reduction may be due to retinal disease or due to abnormalities of the optic pathway including brain tumours. The Delphi panel agreed that, even in the absence of other symptoms and signs, a reduction in visual acuity increased the likelihood of an underlying CNS lesion to such an extent that CNS imaging is required. See above for the frequencies of reduced visual acuity in the meta-analysis and cohort study.

Proptosis

<i>Strength of evidence</i>	<i>4</i>
<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	<i>87% (original Delphi round 1)</i>

Rationale

In a recent series of children with proptosis over a third had malignant disease and 14% had an optic pathway tumour [173]. In all these cases orbital and CNS imaging was an important component of the diagnostic assessment for these children. The Delphi panel agreed that, even in the absence of other symptoms and signs, proptosis increased the likelihood of an underlying CNS lesion to such an extent that CNS imaging is required. 1% of children in the cohort study and 16% of children with neurofibromatosis and a brain tumour in the meta-analysis had proptosis.

New onset paralytic (non-concomitant) squint

<i>Strength of evidence</i>	<i>4</i>
<i>Recommendation form</i>	<i>Conditional</i>

Consensus achieved 90% (original Delphi round 2)

Rationale

Paralytic squint occurs when one of the muscles controlling eye movement is not functioning correctly. This may result from direct muscle damage or abnormality or be due to damage to the innervating nerves, one cause of which is a brain tumour [174]. The Delphi panel agreed that, even in the absence of other symptoms and signs, a new onset paralytic squint increased the likelihood of an underlying CNS lesion to such an extent that CNS imaging is required. See above for the frequencies of abnormal eye movements (includes squint) in the meta-analysis and cohort study.

A visual abnormality with 1 or more other symptom/sign suggestive of a brain tumour

Strength of evidence 4

Recommendation form Conditional

Rationale

The Guideline Development Group and revision workshop group agreed that as per the symptom card, any child with 2 or more symptoms listed in the presentation section of this guideline should have an MRI scan. The Delphi group reached consensus on the statement regarding nausea/vomiting plus another symptom and this was editorially agreed to be implemented across the guideline for all symptoms.

5.1.4e Motor symptoms and signs

Consider a brain tumour in any child presenting with a persisting motor abnormality. Any motor abnormality lasting longer than two weeks should be regarded as persistent.

Strength of evidence 2++

Recommendation form Strong

Consensus achieved 91% (original Delphi round 1)

Rationale

Depending on patient age and tumour location between 10% and 78% of children reported in the meta-analysis had a motor system abnormality at diagnosis [2]. In the cohort study 22% of children at symptom onset and 67% by diagnosis had a motor system abnormality [1]. The Delphi panel agreed that if a motor abnormality persisted for more than two weeks then the likelihood of an underlying brain tumour is increased and this should be considered in the differential diagnosis. The revision workshop group agreed that this was valid.

A history of a change or deterioration in motor skills may indicate a brain tumour e.g. change in hand or foot preference, developmental regression, change in gait, difficulties with balance

Strength of evidence 3

Recommendation form Conditional

Consensus achieved 91% (revision Delphi round 1)

Rationale

4% of children in the cohort study had developmental regression (includes motor skill regression) by diagnosis [1].

History should enquire into subtle changes in motor skills e.g. loss of learned skills (computer games, sport, handwriting)

Strength of evidence 3

Recommendation form *Conditional*
Consensus achieved *91% (revision Delphi round 1)*

Rationale

Individual case reports and professional experience has demonstrated that the changes in motor skills that may occur with a brain tumour can be subtle and identification may require detailed assessment. The research team, Delphi workshop and Delphi panel felt that it was important to highlight this so that any subtle change is specifically asked about.

Assessment of a child's fine motor and visual-motor skills should include questioning or observation of:

Sitting and crawling in infants

Strength of evidence *4*
Recommendation form *Conditional*
Consensus achieved *95% (original Delphi round 1)*

Walking and running

Strength of evidence *4*
Recommendation form *Conditional*
Consensus achieved *95% (original Delphi round 1)*

Coordination e.g. heel to toe walking

Strength of evidence *4*
Recommendation form *Conditional*
Consensus achieved *95% (original Delphi round 1)*

Handling of small objects

Strength of evidence *4*
Recommendation form *Conditional*
Consensus achieved *97% (revision Delphi round 1)*

Handwriting in school age children

Strength of evidence *4*
Recommendation form *Conditional*
Consensus achieved *97% (revision Delphi round 1)*

Rationale

To undertake a complete motor assessment it is important to assess gross and fine motor skills and motor coordination as a brain tumour may cause an abnormality in one of these areas without affecting the others. The revision workshop group highlighted that it was not always possible to observe all of these within the consultation due to a combination of factors. The Delphi panel agreed that observing or questioning the above would allow adequate assessment of a child presenting with symptoms or signs that might be due to a brain tumour.

Delayed diagnosis has been associated with:

- **Attributing abnormal balance or gait to middle ear disease in the absence of corroborative findings**

Strength of evidence *3*
Recommendation form *Conditional*
Consensus achieved *89% (original Delphi round 1)*

Rationale

The Delphi panel agreed that in the absence of corroborative findings abnormal balance or gait should not be attributed to middle ear disease. The guideline team felt that this presentation

needed to be highlighted as failure to consider a central cause of abnormal balance or gait, particularly in young children, has been associated with a prolonged symptom interval and diagnostic difficulties.

- **Failure to identify swallowing difficulties as the cause of recurrent chest infections or “chestiness”**

Strength of evidence 3

Recommendation form Conditional

Consensus achieved 78% (original Delphi round 1)

Rationale

Young children with swallowing difficulties frequently present with recurrent chest infections or chest symptoms without evidence of overt infection (“chestiness”). Whilst swallowing difficulties are an infrequent presentation of brain tumours (5% of cohort study at diagnosis) the guideline development team felt that this presentation needed to be highlighted as it has been associated with a prolonged symptom interval and diagnostic difficulties.

CNS imaging required for children with new onset focal neurological signs including:

A regression in motor skills

Strength of evidence 4

Recommendation form Strong

Consensus achieved 91% (revision Delphi round 1)

Rationale

Motor skill regression may occur with brain tumours. See above for frequencies in cohort study. The presence of a persistent regression in motor skills increases the likelihood of an underlying CNS lesion, including a brain tumour; to such an extent that the Delphi panel agreed that CNS imaging is required even in the absence of other symptoms and signs.

Focal motor weakness

Strength of evidence 4

Recommendation form Strong

Consensus achieved 91% (revision Delphi round 1)

Rationale

Brain tumours may cause focal motor weakness (5% and 19% of children in the meta-analysis). The presence of focal motor weakness increases the likelihood of an underlying CNS lesion, including a brain tumour, to such an extent that the Delphi panel agreed that CNS imaging is required even in the absence of other symptoms and signs.

Abnormal gait and / or coordination (unless local cause)

Strength of evidence 4

Recommendation form Strong

Consensus achieved 91% (revision Delphi round 1)

Rationale

Between 7% and 78% of the children in the meta-analysis had abnormal gait at diagnosis and in the cohort study 12% of children at symptom onset and 45% by diagnosis had an abnormal gait or coordination difficulties. Unless there is an obvious local cause (e.g. local trauma, joint infection or inflammation) the presence of abnormal gait or coordination difficulties increases the likelihood of an underlying CNS lesion, including a brain tumour, to such an extent that the

Delphi panel agreed that CNS imaging is required even in the absence of other symptoms and signs.

Bell's palsy (isolated lower motor facial palsy) with no improvement within 4 weeks

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	<i>Conditional</i>
<i>Consensus achieved</i>	75% (original Delphi round 2)

Rationale

New onset facial nerve paralysis in children has large differential diagnosis including trauma, infection, intracranial tumour, hypertension, toxins and myasthenia gravis [140, 141]. The majority of cases are presumed to be due to infection and should show improvement within 4 weeks. 15% of children with a brain stem tumour in the meta-analysis had a facial palsy at diagnosis. In the cohort study 3% of children at symptom onset and 14% at diagnosis had a facial palsy. A facial palsy that does not show improvement within 4 weeks increases the likelihood of an underlying CNS lesion, including a brain tumour, to such an extent that the Delphi panel agreed that CNS imaging is required even in the absence of other symptoms and signs.

Swallowing difficulties (unless local cause)

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	<i>Strong</i>
<i>Consensus achieved</i>	91% (revision Delphi round 1)

Rationale

Swallowing difficulties may be caused by a brain tumour. See above for frequencies in the cohort study. The presence of swallowing difficulties without an obvious local cause increases the likelihood of an underlying CNS lesion, including a brain tumour, to such an extent that the Delphi panel agreed that CNS imaging is required even in the absence of other symptoms and signs.

Persistent head tilt (unless local cause)

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	<i>Strong</i>
<i>Consensus achieved</i>	91% (revision Delphi round 1)

Rationale

The guideline development group, in consultation with healthcare professionals and families affected by a brain tumour diagnosis, have identified head tilt as a specific symptom of brain tumour which they believe requires highlighting. Children with posterior fossa tumours can present with head tilt. This is a presentation that was identified in the cohort study as being associated with a delayed diagnosis [1]. Initially the guideline development group felt that this would be included in the focal motor deficit section of the guideline however, given the particular association of head tilt with a prolonged symptom interval, the development group have decided to provide specific advice for this presentation.

A motor abnormality with one or more other symptoms suggestive of a brain tumour

<i>Strength of evidence</i>	4
<i>Recommendation form</i>	<i>Strong</i>

Rationale

The Guideline Development Group and revision workshop group agreed that as per the symptom card, any child with 2 or more symptoms listed in the presentation section of this guideline should have an MRI scan. The Delphi group reached consensus on the statement

regarding nausea/vomiting plus another symptom and this was editorially agreed to be implemented across the guideline for all symptoms.

5.1.4f Growth and endocrine

Consider a brain tumour in any child presenting with any two of the following:

Growth failure

Delayed or arrested puberty

Polyuria and polydipsia

Galactorrhoea

Primary/secondary amenorrhoea

Strength of evidence 2++

Recommendation form Strong

Consensus achieved 84% (original Delphi round 3)

Rationale

See above for frequencies of the above symptoms and signs in the meta-analysis and cohort study. There are many causes for the above symptoms and signs in childhood however the triad of growth failure, delayed or arrested puberty and diabetes insipidus is characteristic of central brain tumours involving the hypothalamus and / or pituitary areas. In view of this the guideline development group felt it was important to highlight this specific combination of symptoms and signs and the Delphi panel agreed with this.

If the history raises any concern, including parental concern about any aspect of growth, the child's height weight and head circumference (if under 2 years of age) should be measured and plotted on a growth chart.

Strength of evidence 4

Recommendation form Conditional

Consensus achieved 98% (revision Delphi round 2)

Rationale

The workshop panel highlighted again, that parental concern regarding growth was important to take seriously. In these cases the growth should be measured and plotted to assess value of their concern. The Delphi panel agreed that this should be standard practice.

A child with a height or weight outside the normal range (<0.4th or >99.8th centiles, crossing centiles due to increased or decreased velocity outside that expected for age/pubertal stage or parental target range) should be referred to secondary care for assessment of their growth (see centile charts).

Strength of evidence 4

Recommendation form Conditional

Consensus achieved 84% (revision Delphi round 1)

Rationale

The workshop group felt it was necessary to define growth failure for those reading the guideline to aid referral. The Delphi panel agreed that these children should be referred for assessment of growth.

Brain tumours can present with rapid weight loss or faltering growth, however differential diagnosis when presented with this symptom is wide. If a young person presents with rapid

weight loss/underweight, a careful assessment should be undertaken looking for the other signs and symptoms of a brain tumour.

Strength of evidence 2++
Recommendation form Conditional
Consensus achieved 86% (revision Delphi round 2)

Rationale

The guideline development group have analysed HeadSmart data looking at the groups which have longest delays in diagnosis. The two groups highlighted were teenagers/young people and those with supratentorial midline such as craniopharyngiomas and optic pathway gliomas. These children can present initially with growth problems prior to acquisition of other symptoms as these subtypes of tumours are slow-growing. The Delphi panel agreed that young people in particular, presenting with growth problems should be carefully assessed for other signs and symptoms of a brain tumour.

Early referral (from primary care) is required for a child presenting with:

- Precocious puberty**
- Delayed or arrested puberty**
- Growth failure**
- Galactorrhoea**
- Primary/secondary amenorrhoea**
- Polyuria/polydipsia**

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 88% (revision Delphi round 1)

Rationale

Children presenting with the above symptoms and signs require investigation to determine the underlying cause. Due the wide differential diagnosis the Delphi panel felt that this should be undertaken in secondary care.

Tumours affecting the midline supratentorial part of the brain can also affect vision. Children presenting with the above symptoms require a full visual assessment.

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 82% (revision Delphi round 1)

Rationale

Looking at our HeadSmart data, those with supratentorial midline such as craniopharyngiomas and optic pathway gliomas have longest delays to diagnosis. The most devastating consequence of these benign tumours is blindness. The Delphi panel agreed that all children presenting with the list of endocrine symptoms mentioned above require a visual assessment which would aid earlier diagnosis.

Early specialist referral for consideration of underlying causes including CNS causes is required for a child presenting with precocious puberty.

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 76% (original Delphi round 3)

Rationale

Precocious puberty has multiple causes including brain tumours [175]. Assessment of children with precocious puberty is complex and therefore the Delphi panel felt that such children merited early specialist assessment (usually by a paediatric endocrinologist) for determination of the underlying cause.

Diabetes insipidus must be considered in a child presenting with polyuria and / or secondary nocturnal enuresis.

Strength of evidence 4
Recommendation form Conditional
Consensus achieved 89% (original Delphi round 2)

Whilst other causes of polyuria and secondary nocturnal enuresis (e.g. urinary tract infection, diabetes mellitus, and behavioural difficulties) are more common in children it is important to include diabetes insipidus in the differential diagnosis. Diabetes insipidus may be due to renal or central (including brain tumours) causes. The Delphi panel felt that it was important to highlight this presentation as it has been associated with a prolonged symptom interval and diagnostic difficulties in children with central brain tumours.

Delayed diagnosis has been associated with:

- **Attributing impaired growth plus vomiting to gastrointestinal disease in the absence of corroborative findings.**

Strength of evidence 3
Recommendation form Conditional
Consensus achieved 85% (original Delphi round 1)

Rationale

The Delphi panel agreed that in the absence of corroborative findings impaired growth and vomiting should not be attributed to gastrointestinal disease. The guideline team felt that this presentation needed to be highlighted as failure to consider a central cause, particularly in young children, has been associated with a prolonged symptom interval and diagnostic difficulties.

- **Failure to consider diabetes insipidus in children with polyuria and polydipsia**

Strength of evidence 3
Recommendation form Conditional

Rationale

The Guideline development team felt that this point should be highlighted as it has been associated with diagnostic difficulty and a very prolonged symptom interval in some children.

- **Failure to consider a brain tumour in young people with symptoms suggestive of an eating disorder**

Strength of evidence 4
Recommendation form Conditional

Rationale

The Guideline development team felt that this point should be highlighted as there have been cases where young people have had a very prolonged symptom interval after being diagnosed initially with an eating disorder. In order to make these areas easy to identify in the guideline

they have been headed with the caption “Delayed diagnosis has been associated with:” and was therefore not sent to the Delphi group.

- **Failure to assess vision in children presenting with growth and/or endocrine symptoms**

Strength of evidence 3

Recommendation form Conditional

Rationale

The Guideline development team felt that this point should be highlighted as it has been associated with diagnostic difficulty and a very prolonged symptom interval in some children. In order to make these areas easy to identify in the guideline they have been headed with the caption “Delayed diagnosis has been associated with:” and was therefore not sent to the Delphi group.

CNS imaging required for children with new onset focal neurological signs including:

An endocrine or growth abnormality with 1 or more other symptom suggestive of a brain tumour

Strength of evidence 4

Recommendation form Conditional

Rationale

The Guideline Development Group and revision workshop group agreed that as per the symptom card, any child with 2 or more symptoms listed in the presentation section of this guideline should have an MRI scan. The Delphi group reached consensus on the statement regarding nausea/vomiting plus another symptom and this was editorially agreed to be implemented across the guideline for all symptoms.

5.1.4g: Behaviour

Brain tumours can manifest as with neuropsychiatric symptoms including new onset mood disturbance, withdrawal, disinhibition and pervasive lethargy. All children with these symptoms require careful assessment looking for the other signs and symptoms of a brain tumour.

Strength of evidence 2++

Recommendation form Strong

Consensus 95% (revision Delphi round 2)

Rationale

Up to 21% of children with a brain tumour in the meta-analysis experienced lethargy at diagnosis. In the cohort study 3% of children at symptom onset and 19% at diagnosis experienced lethargy. In the initial cohort study lethargy was the commonest behavioural abnormality identified. In the new systematic review, there was a pooled proportion of 2% presenting with a behavioural problem. The Guideline development team wanted to highlight lethargy in children with brain tumours as failure to recognise lethargy as a symptom has been associated with diagnostic difficulty and a prolonged symptom interval, however also recognised that other neuro-psychiatric symptoms were important to consider.

Delayed diagnosis has been associated with:

- **Attributing behavioural change in young people to “normal adolescent behaviour”**
- **Attributing mood disturbances to a psychiatric cause without full physical assessment**

Strength of evidence 4

Recommendation form Conditional

Rationale

The Guideline development team felt that this point should be highlighted lethargy and other behaviour change are under-recognised symptoms of brain tumours in childhood. The Guideline Development Group could recall cases where delays in diagnosis have occurred due to behavioural change being thought as normal for that age and so it was felt to be important to highlight in this guideline.

5.2 Summary of recommendations for healthcare professionals

The guideline development group has also developed quick reference guide, a one page summary of guideline recommendations and signs and symptoms children with brain tumours develop by subspecialty for healthcare professionals (see Appendix 1).

5.3 Guideline summary for parents and young people

Educating parents and young people about the symptoms associated with brain tumours and providing guidance as to how and when to seek help with these symptoms is an important method of guideline implementation. The guideline development group have developed a summary for non-healthcare professionals that describes the symptoms and signs children with brain tumours develop and advises how and when to seek help. The summary is designed to be presented as a fold up card with specific symptom and sign information on the front and more general advice and information on the back. The front and back of the summary cards is shown in Appendix 2.

6 IMPLEMENTATION STRATEGY AND FUTURE WORK

6.1 Guideline implementation

6.1.1 Implementation

The original guideline implementation was supported with the launch of the HeadSmart: Be Brain Tumour Aware campaign (www.headsmart.org.uk) including a website and educational package which we feel has reduced professional reluctance to guideline implementation due to a perceived risk of increased (unnecessary) imaging or increased anxiety. We have also shown a reduction in the total diagnostic interval across the UK which has encouraged further use of the guideline.

This is a revision of the original guideline and so we feel that it will continue to be used in practice. We will also continue to monitor total diagnostic interval (TDI, time from symptom onset to diagnosis) using the same methodology published previously [3].

6.1.2 Consideration of health benefits, side effects and risks

The risks and benefits of guideline implementation have been carefully considered by the development group. An earlier diagnosis in children with brain tumours should lead to reduce long term effects (reduced cognitive deficits, reduced endocrinopathies, improved vision). This is likely to have benefit for the individual, their family / carers and the state (reduced dependence on state support and increased ability to work). These benefits are hard to quantify.

There is a risk that guideline implementation may lead to increased numbers of children referred for CNS imaging. The guideline recommends that children be imaged with MRI, which avoids the risk of exposure to ionising radiation, however increased demand for imaging could theoretically overwhelm services. In order to minimise this risk, the indications for imaging advised by the guideline have been reviewed and agreed upon by over 100 doctors from primary, secondary and tertiary care.

As the majority of doctors agreed with the recommendations for imaging, it is likely that children presenting with these signs and symptoms would undergo imaging at some stage and that the main effect of guideline implementation will be to decrease the time to imaging for children requiring this rather than increase the total number of children undergoing brain imaging.

Since the initial publication of the guideline, a national public and professional awareness campaign called HeadSmart: Be Brain Tumour Aware was launched in 2011 to amplify the guideline. The total diagnostic interval (TDI), which is defined as the time from symptom onset to diagnosis, across the UK has been monitored since 2006 (pre-guideline) to 2013 (2 years post HeadSmart launch). There has been a statistically significant reduction from a median TDI of 14.4 weeks to 6.7 weeks ($p < 0.001$). Whilst this cannot be directly attributed to the guideline or campaign, we know that the TDI remained stable prior to publication of this guideline and this is the only intervention known to have occurred in this timeframe [3]. (See Appendix 10 for full publication list).

6.1.3 Facilitators and barriers

Many of the potential benefits of earlier diagnosis of brain tumours, such as reduced morbidity and dependency on state support, may not be apparent until years after diagnosis and treatment; it is therefore difficult to quantify these.

The major barrier to implementation of this guideline is likely to be a perceived or actual increase in numbers of children referred for CNS imaging. This was set as the greatest risk at the outset and introduced *reassurance* as a major part of the guideline's content and dissemination via the website and associated materials. We have not seen surges in referral during the previous period.

There is also a risk that referring children for imaging who subsequently do not have a brain tumour could lead to unnecessary anxiety for both the patient and their families. Most families and patients presenting with the signs and symptoms detailed in the guideline are concerned that they / their child has a serious underlying illness and find a structured investigation of potential causes minimises their anxiety.

6.2 Costs and benefits of implementation

As many of the potential benefits of earlier diagnosis of brain tumour may not be obvious until years after diagnosis and treatment, it is difficult to quantify the financial gains and costs of guideline implementation. The major organisational and financial barriers to implementation are likely to be a perceived or actual increase in children referred for CNS imaging. As discussed above, the recommendations for imaging have been agreed upon by doctors from primary, secondary and tertiary care and, by representing best practice, are unlikely to lead to a large increase in the number of children referred for imaging. This was discussed again as part of the 2016 update during the revision multi-disciplinary workshop. It was agreed that these children would eventually get scanned if the symptoms persisted so as opposed to increasing the number of scans, we are pushing forward the time to scan.

The GDG is working with the University of Nottingham to quantify MRI imaging pre- and post-guideline development and preliminary data does not suggest a surge in scan requests. The data analysis is currently in process and this data will be extremely useful to allay any fears regarding increase in organisational pressure.

Furthermore, by increasing awareness of childhood brain tumours, the educational package and website should reduce professional reluctance to guideline implementation due to a perceived risk of increased (unnecessary) imaging.

6.3 Further review policy

The guideline is a stand-alone guideline written by the Guideline Development Group (GDG) of the Children's Brain Tumour research Centre (CBTRC) at the University of Nottingham.

To ensure it provides high quality evidence to healthcare professionals across the country, this guideline requires 5 yearly review and revision. The following processes will need to be followed by the GDG when review is required.

The process of review and revision involves a number of steps, which are outlined below and will take on average 9-12 months to complete. The methodology should be the same as previous reviews, however may change if new evidence suggests a more robust method to follow.

1. A systematic review and meta-analysis of the presenting signs and symptoms of brain tumours in children
2. A multi-disciplinary workshop discussing the existing guideline and any new evidence found in the systematic review
3. A modified Delphi consensus process may or may not be required depending on the outcome of the discussions at the multi-disciplinary workshop.

Once these steps have been completed, an addendum will be written which will include the methodology, results, quick reference guide and full guideline. The full guideline should outline the levels of evidence and grading recommendation using the most up to date SIGN (Scottish Intercollegiate Guideline Network) guidance [156]. The guideline will then be sent to RCPCH for endorsement and also to NICE re-accreditation with the supporting paperwork.

What if there are developments in between the 5 year timeframe?

The GDG also need to be aware that new evidence which may or may not be critical may become available in the interim period between reviews.

If this were to happen, the GDG will need to organise a multi-disciplinary team including parent representatives to discuss the new evidence and decide whether or not it needs to be included in the guideline urgently.

If the evidence needs to be included, a few options are available. If the timing of such is 4 years after previous review, the whole review process as outlined above can take place. If the timing is less than 4 years then the level of evidence attributed to the new evidence needs to be considered. In most cases the evidence will need to be passed through a modified Delphi consensus process in order to be included within the guideline. If the level of evidence is deemed high enough to allow direct entry into the guideline without a modified Delphi consensus then the reasons for this should be outlined in the addendum document.

REFERENCES

1. Wilne, S. et al. *The presenting features of brain tumours: a review of 200 cases*. Archives of Disease in Childhood, 2006. 91(6): p. 502-506.
2. Wilne, S. et al. *Presentation of childhood CNS tumours: a systematic review and meta-analysis*. The Lancet Oncology, 2007. 8(8): p. 685-695.
3. HeadSmart: Be Brain Tumour Aware. *A new clinical guideline from the Royal College of Paediatrics and Child Health with a national awareness campaign accelerates brain tumor diagnosis in UK children – "HeadSmart: Be Brain Tumour Aware."* Neuro-Oncology. 2015; 0-1-10; doi:10.1093/neuonc/nov187.
4. Kameda-Smith, MM. et al. *Time to diagnosis of paediatric posterior fossa tumours: an 11-year West of Scotland experience 2000-2011*. Br J Neurosurg. 2012. 27:364-
5. Shay, V. et al. *Diagnostic delay of paediatric brain tumors in Israel: a retrospective risk factor analysis*. Child Nerv Syst. 2012. 28:93-100.
6. Klitbo, D.M. et al. *Symptoms and time to diagnosis in children with brain tumours*. Danish Medical Bulletin. 2001.
7. Brasme, J-F. et al. *Interval between onset of symptoms and diagnosis of medulloblastoma in children: distribution and determinants in a population based study*. Eur J Pediatr. 2012. 171:25-32.
8. Hayashi, N. et al. *How do clinical features of brain tumours in childhood progress before diagnosis?* Brain and Development. 2010. 32:636-641.
9. Badr, H. et al. *Latency of Paediatric Brain Tumors Diagnosis in Province of Delta, a Team Experience*. Egypt J. Neurol. Pscyat. Neurosurg. 2009.
10. Wilkening, G.N. et al. *Memory disorders in children with central nervous system germ cell tumours*. Journal of Pediatric Oncology Nursing. 2012.
11. Mauffrey, C. *Paediatric brainstem gliomas: prognostic factors and management*. Journal of Clinical Neuroscience. 2006; 13: 431-437.
12. Caldarelli, M. et al. *Long term results of the surgical treatment of craniopharyngioma: the experience at the Poloclinico Gemelli, Catholic University, Rome*. Childs Nerv Syst. 2005. 21: 747-757.
13. Ersahin, Y. et al. *Craniopharyngiomas in children: Turkey experience*. Childs Nerv Syst. 2005; 21: 766-772.
14. Stark, A. M. et al. *Management of tectal glioma in childhood*. Journal of Paediatric Neurology. 2005.
15. Cuccia, V. et al. *Pinealoblastomas in children*. Childs Nerv Syst. 2006: 22:577-585.
16. Avile de Espindola et al. *Brain tumors in the first three years of life: a review of twenty cases*. Arq Neuropsiquiatr. 2007; 65:960-964.
17. Baussard, B. et al. *Pediatric infratentorial gangliogliomas: a retrospective series*. J neurosurg. 2001; 107: 286-291.
18. Li, X. Zhao, J. *Intracranial meningiomas of childhood and adolescence: report of 34 cases with follow up*. Childs Nerv Syst. 2009: 1411-1417.
19. Tang, J. et al. *The germinomas arising from the basal ganglia and thalamus*. Childs Nerv Syst. 2008. 24:303-306.
20. Zuccaro, G. Sosa, F. *Cerebellopontine angle lesions in children*. Childs Nerv Syst. 2007. 23:177-183.
21. Mehrotra, N. et al. *Intracranial tumors in the first year of life: the CHEO experience*. Childs Nerv Syst. 2009. 25:1563-1569.

22. Taylor, M.T. et al. *Hypothalamic-Pituitary lesions in Pediatric patients: endocrine symptoms often precede neuro-ophthalmic presenting symptoms*. The Journal of Pediatrics. 2012. 161:855-63.
23. Wilne, S. et al. *Progression from first symptom to diagnosis in childhood brain tumours*. Eur J Pediatr. 2012. 171:87-93.
24. Gucev, Z.S. *Childhood craniopharyngioma in Macedonia: incidence and outcome after subtotal resection and cranial irradiation*. World J Pediatr. 2011.
25. Jaing, T-H. et al. *Intracranial tumors in infants: a single institution experience of 22 patients*. Child Nerv Syst. 2011. 27:415-419.
26. Ogiwara, H. et al. *Choroid plexus tumors in pediatric patients*. British Journal of Neurosurgery. 2012. 26:32-37.
27. Lang, S.S et al. *Surgical treatment of brain tumors in infants younger than 6 months of age and review of the literature*. World Neurosurgery. 2012. 78; 137-144.
28. Nielsen, E.H. et al. *Acute presentation of craniopharyngioma in children and adults in a Danish national cohort*. Pituitary. 2012. 16:528-535.
29. Das, K.K. et al. *Pediatric glioblastoma: clinic-radiological profile and factors affecting the outcome*. Child Nerv Syst. 2012. 28:2055-2062.
30. Sun, T. et al. *Clinical outcomes and natural history of pediatric brainstem tumors: with 33 case follow ups*. Neurosurg Rev. 2012. 36:311-320.
31. Lohmann, D.J.A. et al. *Most central nervous system tumours in children are diagnosed with little delay after admission*. Dan Med J. 2012.
32. Rath, S.R. et al. *Childhood craniopharyngioma: a 20 year institutional experience in Western Australia*. Journal of Paediatrics and Child Health. 2013. 49: 403-408.
33. Goodden, J. et al. *The role of surgery in optic pathway/hypothalamic gliomas in children*. J Neurosurg Pediatrics. 2014. 13:1-12.
34. Sinha, S. et al. *Pediatric giant pituitary adenomas: are they different from adults? A clinical analysis of a series of 12 patients*. Childs Nerv Syst. 2014. 30:1405-141.
35. Puget, S. et al. *Thalamic tumors in children: a reappraisal*. J Neurosurg. 2007. 106:354-362.
36. Biswas, A. et al. *Intracranial atypical teratoid rhabdoid tumor: current management and a single institute experience of 15 patients from north india*. Acta Neurochir. 2015. 157:589-596.
37. Leroy, H-A. et al. *Anorexia: an early sign of fourth ventricle astrocytoma in children*. Childs Nerv Syst. 2014. 30:2089-2095.
38. Qaddoumi, I. et al. *Characterization, treatment and outcome of intracranial neoplasms in the first 120 days of life*. Journal of Child Neurology. 2011.
39. Garzon, M. et al. *Brainstem tumors in children and adolescents: single institutional experience*. Childs Nerv Syst. 2013. 29:1321-1331.
40. Koh, E.J. et al. *Clinical outcome of pediatric choroid plexus tumors: retrospective analysis from a single institute*. Child Nerv Syst. 2014. 30:217-225.
41. Santos, M.V. et al. *Pediatric meningiomas: a single center experience with 15 consecutive cases and review of the literature*. Child Nerv Syst. 2012. 28: 1887-1896.
42. Zhan, R. et al. *Surgical outcomes of endoscopic transsphenoidal route to pituitary tumors in paediatric patients >10 years of age: 5 years of experience at a single institute*. Arch Dis Child. 2015. 100:774-778.
43. Drimtzias, E. et al. *The ophthalmic natural history of paediatric craniopharyngioma: a long-term review*. J Neurooncol. 2014. 120: 651-656.

44. Santos de Oliveira, R. et al. *The impact of surgical resection of giant supratentorial brain tumor in pediatric patients: safety and neurological outcome evaluated in 23 consecutive cases.* Childs Nerv Syst. 2014.
45. Koutourousiou, M. et al. *Endoscopic endonasal surgery for craniopharyngioma: surgical outcome in 64 patients.* J Neurosurg. 2013. 119:1194-1207.
46. Teo, W-Y. et al. *The gut or the brain? – gastrointestinal misdiagnoses of infantile brain tumors.* Childs Nerv Syst. 2014. 30:1449-1453.
47. Ramelli, G. et al. *Age-dependent presentation of Tectal Plate Tumors: preliminary observations.* Journal of Child Neurology. 2011. 26(3): 377-380.
48. Houdemont, S.P. et al. *Short-term neurological outcome of children after surgery for brain tumors: incidence and characteristics in a pediatric intensive care unit.* Childs Nerv Syst. 2011. 27: 933-941.
49. Serowka, K. et al. *Central nervous system tumors in the first six months of life: The Childrens Hospital Los Angeles Experience, 1979-2005.* Pediatric Hematology and Oncology. 2010.
50. Broniscer, A. et al. *Young age may predict a better outcome for children with diffuse pontine glioma.* Cancer. 2008.
51. Cuccia, V. et al. *Pure pineal germinomas: analysis of gender incidence.* Acta neurochir. 2006. 148: 865-871.
52. Ahn, Y. et al. *Optic pathway glioma: outcome and prognostic factors in a surgical series.* Childs Nerv Syst. 2006.
53. Wilne, S.H. et al. *The presenting features of brain tumours: a review of 200 cases.* Arch Dis Child. 2006. 91:502-506.
54. Baroncini, M. et al. *Surgical resection of thalamic tumors in children: approaches and clinical results.* Childs Nerv Syst. 2007. 23:753-760.
55. Pandey, P. et al. *Pediatric pituitary adenoma: a series of 42 patients.* Journal of Clinical Neuroscience. 2005. 12:124-127.
56. De Leon-Bojorge, B. et al. *Central Nervous system atypical teratoid rhabdoid tumor: experience at the National Institute of Pediatrics, Mexico City.* Childs Nerv Syst. 2008. 24:307-312.
57. Perez-Gomez, J.L. et al. *Stereotactic biopsy for brainstem tumors in pediatric patients.* Childs Nerv Syst. 2010. 26: 29-34.
58. De Andrade, F.G. et al. *Intracranial and spinal ependymoma. Series de Faculdade de Medicina, Universidade de Sao Paulo.* Arq Neuropsiquiatr. 2009. 67:626-632.
59. Goyal, N. et al. *Intracranial teratomas in children: a clinicopathological study.* Childs Nerv Syst. 2013. 29: 2035-2042.
60. Ternier, J. et al. *Tectal plate lesions in children.* J Neurosurg. 2006. 104: 369-376.
61. Sonoda, Y. et al. *Germ Cell tumors in the basal ganglia: problems of early diagnosis and treatment.* J Neurosurg Pediatrics. 2008. 2:118-124.
62. Mehta, N. et al. *Meningiomas in children. A study of 18 cases.* Journal of Pediatric Neurosciences. 2009. 4(2): 61-65.
63. Extremera, V.C. et al. *Torticollis is a usual symptom in posterior fossa tumors.* Eur J Pediatr. 2008. 167:249-250.
64. Fernandez, C. et al. *Thalamic gliomas in children: an extensive clinical, neuroradiological and pathological study of 14 cases.* Childs Nerv Syst. 2006. 22:1603-1610.
65. Sandri, A. et al. *Diffuse and focal brainstem tumors in childhood: prognostic factors and surgical outcome.* Childs Nerv Syst. 2006. 22:1127-1135.

66. Meuric, S et al. *Influence of tumor location on the presentation and evolution of craniopharyngiomas*. J Neurosurg. 2005. 103:421-426.
67. Rifi, H. et al. *Medulloblastoma in children: A retrospective Tunisian review*. Pediatric Blood and Cancer. 2011. Vol./is.57/5(882-883), 1545-5009. (abstract only)
68. Chastagner, P. et al. *Primary meningiomas of childhood and adolescence: a series of 104 cases*. Pediatric blood and cancer. 2011. Vol./is. 57/5 (810), 1545-5009.
69. El-Gaidi, M.A. *Descriptive Epidemiology of Pediatric Intracranial Neoplasms in Egypt*. Pediatr Neurosurg. 2011. 47:385-395.
70. Menon, G. et al. *Choroid plexus tumors: an institutional series of 25 patients*. Neurol India. 2010. 58:429-435.
71. Wilne, S et al. *A service evaluation of implementation of RCPCH brain pathways clinical guideline linked to HeadSmart: be brain tumours aware campaign*. Archives of Disease in Childhood. 2012. Vol./is97/(A82),0003-9888.
72. Bettegowda, C. et al. *Treatment of choroid plexus tumors: a 20-year single institutional experience*. J Neurosurg Pediatrics. 2012. 10:398-405.
73. Moiyadi, A. V. et al. *Feasibility of repeat surgery for pediatric brain tumors: an objective assessment of perioperative outcomes*. J Neurosurg Pediatrics. 2012. 10:411-417.
74. Yu, J. et al. *Epidemiology of brain tumors in children aged two years and under: A 10-year single institute study*. Oncology Letters 9: 1651-1656. 2015.
75. Salenave, S. et al. *Macroprolactinomas in Children and Adolescents: factors associated with the response to treatment in 77 patients*. J Clin Endocrinol Metab. 2015. 100(3):1177-1186.
76. Preub, M. et al. *Signs and symptoms of pediatric brain tumors and diagnostic value of preoperative EEG*. Childs Nerv Syst. 2015.
77. Reulecke, B.C. et al. *Brain Tumors in Children: Initial symptoms and their influence on the Time Span between symptom onset and diagnosis*. Journal of Child Neurology. 2008. 23(2): 178-183.
78. Bilginer, B et al. *Thalamic tumors in children*. Childs Nerv Syst. 2014. 30:1493-1498.
79. Meng, X. et al. *Brain Tumors in children under 3 years old – a retrospective study*. Child's Nervous System. 2012. Vol./is. 28/9(1612), 0256-7040. (abstract only)
80. Lulla, R. et al. *Primary thalamic tumors of astrocytic origin: A 20-year experience at children's memorial hospital*. Neuro-oncology. 2012. Vol./is. 14/(i64-i65). 1522-8517. (abstract only)
81. Ormandy, D. et al. *Outcomes for craniopharyngiomas diagnosed in the North West region of the UK during 1954-2008*. Neuro-oncology. 2012. Vol./is. 14/(i25), 1522-8517. (abstract only)
82. Maza, I. et al. *Epidemiology and treatment outcome of childhood astrocytomas: A single institution 10-year of pediatric oncology unit of Rebagluti Hospital in Lima, Peru*. Neuro-oncology. 2012. Vol./is. 14 (i110), 1522-8517. (abstract only)
83. El-Shazly et al. *Central nervous system tumors in children of Northern Egypt*. Neuro-oncology. 2012. Vol./is.14/(i107), 1522-8517. (abstract only)
84. Bizzi, J.W.J. et al. *Surgery for intracranial tumors in children under 3 years of age*. Child's Nervous system. 2012. Vol./is 28/5(778), 0256-7040.
85. Kiehna, E.N. et al. *The role of transsphenoidal surgery in the management of pediatric prolactinoma*. Child's Nervous System. 2014. Vol./is. 30/11 (1931-1932), 0256-7040. (abstract only)

86. Matushita, H. et al. *Ventral midbrain tumors in children*. Child's Nervous System. 2014. Vol./is.30/11 (1929), 0256-7040. (abstract only)
87. Jaque, F.A.M. et al. *Pediatric central nervous system tumors in New Zealand: a retrospective review from the starship children's hospital*. Child's Nervous System. 2014. Vol./is.30/11 (1926), 0256-7040. (abstract only)
88. Miki, N. et al. *High-dose cabergoline treatment of childhood and adolescence-onset prolactinomas*. Endocrine reviews. 2013. Vol./is. 34/3 SUPPL. 1, 0163-769X. (abstract only)
89. Moreno, E.M.V. et al. *Craniopharyngioma: 12 years' experience and results in a reference centre*. Endocrine Reviews. 2013. Vol./is. 34/3 SUPPL. 1, 0163-769X. (abstract only)
90. Pinarli, F.G. et al. *Institutional experience of paediatric high-grade central nervous system tumours: an analysis of 74 patients and review of the literature*. Wspolczesna Onkol. 2012. 16(1):26-33.
91. Tabatabaei, S.M. et al. *Posterior Fossa Tumor in Children*. Iran J Child Neurology. 2012. 6(2): 19-24.
92. Griessenauer, C.J. et al. *Pediatric tectal plate gliomas: clinical and radiological progression, MR imaging characteristics, and management of hydrocephalus*. J Neurosurg Pediatrics. 2014. 13:13-20.
93. Lundar, T. et al. *Neurosurgical treatment of brain tumors in the first 6 months of life: long-term follow-up of a single consecutive institutional series of 30 patients*. Childs Nerv Syst. 2015. 31:2283-2290.
94. Molineus, A. et al. *Time to diagnosis of brain tumors in children: a single-centre experience*. Pediatrics International. 2013. 55: 305-309.
95. Khan, M.A. et al. *Clinical review of pediatric pilocytic astrocytomas treated at a tertiary care hospital in Pakistan*. Surgical Neurology International. 2012.
96. AlKofide, A. et al. *Medulloblastoma in children above 3 years: reporting treatment results from king faisal specialist hospital and research centre, Riyadh, Saudi Arabia*. Pediatric Blood and Cancer. 2014. vol./is.61/(S180), 1545-5009. (Abstract only)
97. Drogosiewicz, M. et al. *Treatment results of diffuse intrinsic pontine glioma (DIPG) in children. One center experience*. Neuro-oncology. 2014. Vol./is. 16/_i45), 1522-8517. (abstract only)
98. Alston, R. et al. *The presenting symptoms and signs for pediatric brain tumours diagnosed in the North-West of England 1954-2008*. Neuro-oncology. 2014. Vol./is. 16/(i27), 1522-8517 (Abstract only).
99. Lanphear, J. et al. *Presenting symptoms of pediatric brain tumors diagnosed in the emergency department*. Pediatric Emergency Care. 2014. Vol./is. 30/2(77-80), 0749-5161; 1535-1815.
100. Vallero, S.G. et al. *Diffuse intrinsic pontine glioma in children and adolescents: a single-center experience*. Childs Nerv Syst. 2014. 30:1061-1066.
101. Garzon, M. et al. *Low-grade gliomas in children: single institutional experience in 198 cases*. Childs Nerv Syst. 2014.
102. Mahvash, M. et al. *Glioblastoma Multiforme in children: report of 13 cases and review of the literature*. Pediatric Neurology. 2011. 45:178-180.
103. Webb, C. et al. *Pediatric Pituitary Adenomas*. Arch Pathol Lab Med. 2008. Vol 132.
104. Cavallo, L.M. et al. *The endoscopic endonasal approach for the management of craniopharyngiomas: a series of 103 patients*. J Neurosurg. 2014. 121:100-113.

105. Stagno, V. et al. *Presentation, pathology, and treatment outcome of brain tumors in 172 consecutive children at CURE Children's Hospital of Uganda. The predominance of the visible diagnosis and the uncertainties of epidemiology in sub-Saharan Africa.* Childs Nerv Syst. 2014. 30:137-146.
106. Ahmed, K.A. et al. *Histologically-proven low grade brainstem gliomas in children: 30-year experience with long-term follow up at Mayo clinic.* Am J Clin Oncol. 2014. 37(1):51-56.
107. Kinoshita, Y. et al. *Pituitary adenomas in childhood and adolescence with a focus on intratumoral haemorrhage.* Pituitary. 2014. 17:1-6.
108. Phi, J.H. et al. *Latency of intracranial germ cell tumors and diagnosis delay.* Childs Nerv Syst. 2013. 29: 1871-1881.
109. Uche, E.O. et al. *Pediatric brain tumors in Nigeria: clinical profile, management strategies, and outcome.* Childs Nerv Syst. 2013. 29:1131-1135.
110. Yang, K. et al. *Endocrine alteration was presented as the first symptom of childhood intracranial tumor.* Chinese journal of contemporary paediatrics. 2006.
111. Greene, S. et al. *Meningiomas in children.* Pediatr Neurosurg. 2008. 44:9-13.
112. Jaing, T-H. et al. *Treatment of Optic Pathway Hypothalamic Gliomas in Childhood: Experience with 18 consecutive cases.* J Pediatr Hematol Oncol. 2008. 30(3).
113. Lasky, J.L. et al. *Congenital brain tumour: cases series and review of the literature.* J Pediatr Hematol Oncol. 2008. 30(4).
114. Lakhdar, F. et al. *Intracranial meningioma in children: Different from adult forms? A series of 21 cases.* Neurochirurgie. 2010. 56: 309-314.
115. Beckwitt Turkel, S. et al. *Symptoms before and after posterior fossa surgery in pediatric patients.* Pediatr Neurosurg. 2012. 48:21-25.
116. Rahman, M.H. et al. *Is Gross total removal necessary for pediatric posterior fossa tumour?* Mymensingh Medical Journal. 2010. 2:239-243.
117. Yang, K. et al. *Clinical and pathological features of intracranial meningiomas in children: a retrospective analysis.* Neural Regen Res. 2006. 1:6.
118. Aissa, N.B. et al. *Pediatric Craniopharyngiomas. Hormone Research in Pediatrics.* 2013. Vol./is. 80/(384), 1663-2818. (abstract only)
119. Fiori, C. et al. *Central nervous system tumor in children in the west of parana-Brazil.* Pediatric Blood and Cancer. 2013. Vol./is 60/(215), 1545-5009. (abstract only)
120. Ronghue, M. et al. *Pediatric Craniopharyngioma: A 30-year retrospective analysis of the west of Scotland experience.* Pediatric Blood and Cancer. 2013. Vol./is. 60/(137-138), 1545-5009. (abstract only)
121. Moiyadi, A.V. et al. *Profile of pediatric brain tumors at a tertiary care neuro-oncology centre- patterns of care and perioperative outcomes.* Child's Nervous System. 2013. Vol./is. 29/9(1766), 0256-7040. (abstract only)
122. Kammler, G. et al. *A heterogeneous group, brain tumors in the first year of life – a report of 25 patients in our institution.* Child's Nervous System. 2013. Vol./is. 29/9 (1763), 0256-7040. (abstract only)
123. Paternoster G. et al. *Bithalamic tumors in children.* Child's Nervous System. 2013. Child's Nervous System. Vol./is.29/9(1736-1737), 0256-7040.
124. Klimo P. et al. *Management and outcome of focal low-grade brainstem tumors in pediatric patients: the St. Jude experience.* J Neurosurg Pediatr. 2013. 11(3): 274-281.
125. Ghodsi M. et al. *Exophytic glioma of the medulla: presentation, management and outcome.* Pediatr Neurosurg. 2013. 49:195-201.

126. Crawford J.R. et al. *CNS germ cell tumor (CNSGCT) of childhood. Presentation and delayed diagnosis.* Neurology. 2007. 68:1668-1673.
127. Katavetin P. et al. *Pituitary adenomas in children and adolescents.* Journal of pediatric endocrinology and metabolism. 2010. 23:427-431.
128. Huang X. et al. *Diagnosis and treatment of intracranial immature teratoma.* Pediatr Neurosurg. 2009. 45:354-360.
129. Kotulska K. et al. *Surgical treatment of subependymal giant cell astrocytoma in tuberous sclerosis complex patients.* Pediatric Neurology. 2014. 50:307-312.
130. Haider I. et al. *Glioblastoma multiforme in children: prognostic factors and survival.* Radiotherapy and Oncology. May 2011. Vol./is.99/(S248), 0167-8140. (abstract only)
131. Fransolet A.C. et al. *Prise en charge du medulloblastome de l'enfant.* Rev Med Liege. 2007. 62(4):200-204.
132. Voirin, J. et al. *Germ-cell tumors of the central nervous system in childhood: retrospective study of 13 patients.* Neurochirurgie 54 (2008) 55-62.
133. Lena, G. et al. *Les oligodendrogliomes supratentoriels de l'enfant.* Neurochirurgie. 2005. 400-409.
134. Rondinelli, P. I. P. *Primary intracranial germ cell tumors in children: evaluation of fourteen cases.* Arq Neuropsiquiatr 2005. 63(3-B):832-836.
135. Villarejo F J. et al. *Brain-stem tumors in children.* Neurochirurgia. 2008. 19:551-555.
136. Lee Y.Y. et al. *Comparison of hypothalamopituitary axis dysfunction of intrasellar and third ventricular craniopharyngiomas in children.* Brain & Development. 2008. 30:189-194.
137. Yazici N. et al. *Pineal Region Tumors in children: A Single Center Experience.* Neuropediatrics. 2009. 40(1); 15-21.
138. Shamji M F. et al. *Congenital Tumors of the Central Nervous System: The MCH experience.* Pediatric neurosurgery. 2009. 45:368-374.
139. El-Gaidi M A. et al. *Infantile Intracranial Neoplasms: Characteristics and surgical Outcomes of a Contemporary Series of 21 Cases in an Egyptian Referral Center.* Pediatric Neurosurgery. 2010. 46:272-282.
140. Jung T-Y et al. *Endocrinology Outcomes of Pediatric Craniopharyngiomas with anatomical pituitary stalk preservation: a preliminary study.* Pediatric Neurosurgery. 2010. 46: 205-212.
141. Tufan K. et al. *Intracranial meningiomas of childhood and adolescence.* Pediatric Neurosurgery. 2005. 41(1):1-7.
142. Liu ZX et al. *Surgical treatment of childhood craniopharyngioma: clinical analysis of 31 cases.* Zhongguo dangdai erke zazhi. 2009. 11(8):663-665.
143. Liu Y et al. *Analysis of ocular changes in children craniopharyngioma.* Zhonghua yanke zazhi. 2014. 50(5): 355-359.
144. Defoort-Dhellemmes S. et al. *Craniopharyngioma: ophthalmological aspects at diagnosis.* Journal of Pediatric Endocrinology and Metabolism. 2006. 19; 321-324.
145. Di Battista E et al. *Endocrine and growth features in childhood craniopharyngioma: a mono-institutional study.* Journal of Pediatric Endocrinology & Metabolism. 2006. 19: 431-437.
146. Navas-Garcia M et al. *Tumores de la region pineal en la edad pediatrica. Presentacion de 23 casos y revision de la bibliografia.* Rev Neurol. 2011. 52(11):641-652.
147. Sanchez J F C. et al. *Presenting signs and symptoms of central nervous system tumors according to age.* An Pediatr (Barc). 2007. 66(2): 115-20.

148. Roman S V. et al. *Sintomas y signos iniciales de los tumores cerebrales pediatricos*. Neurologia. 2008. 23(4): 215-219.
149. Kolouskova S. et al. *Retrospective analysis of growth in Tumors of Hypothalamus-Hypophysis Region*. Ces-Slov. Pediat. 2005. 60(6):345-348.
150. Zalewska-Szewczyk B. et al. *Prognosis of clinical course of primary brain tumours in children in relationship to the duration and characteristic features of initial clinical symptoms*. Medycyna Wieku Rozwojowego. 2005. 9(3): 567-578.
151. Mohanty C B. et al. *Brain tumors of infancy – an institutional experience and review of the literature*. Pediatr Neurosurg. 2013. 49:145-154.
152. Moher, D. et al. *Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses*. Lancet, 1999. 354(9193): p. 1896-900.
153. Fink, A. et al. *Consensus methods: characteristics and guidelines for use*. American Journal of Public Health, 1984. 74(9): p. 979-83.
154. Hasson, F., Keeney, S. and McKenna, H. *Research guidelines for the Delphi survey technique*. Journal of Advanced Nursing, 2000. 32(4): p. 1008-15.
155. Jones, J. and Hunter, D. *Consensus methods for medical and health services research*. BMJ, 1995. 311(7001): p. 376-80.
156. Scottish Intercollegiate Network. A guideline developer's handbook SIGN. 2015.
157. Report of the Independent Cancer Taskforce. *Achieving World-Class Cancer Outcomes: A Strategy for England 2015-2020*.
http://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf
158. Thulesius, H., Pola, J. and Hakansson, A. *Diagnostic delay in pediatric malignancies--a population-based study*. Acta Oncologica, 2000. 39(7): p. 873-6.
159. Comi, A.M. et al. *Clinical and neuroradiologic findings in infants with intracranial ependymomas*. Pediatric Oncology Group. Pediatric Neurology, 1998. 18(1): p. 23-9.
160. Royal College of Radiologists. iRefer: Making the best use of clinical radiology. 7th Edition. 2011 <http://nww.irefer.nhs.uk/>
161. National Institute for Clinical Excellence. *Suspected cancer: recognition and referral*. 2015. The National Collaborating Centre for Primary Care.
162. National Institute of Clinical Excellence. *The epilepsies: The diagnosis and management*. 2016.
163. Stiller, C. *Epidemiology in Brain and Spinal Tumours of Childhood*. Editors Walker, D., Perilongo, G., Punt, J. and Taylor, R. 2005. Arnold: London.
164. National Institute for Clinical Excellence. *Headaches in over 12s: diagnosis and management*. 2012.
165. *Cancer: Clinical Features and Management* in Oxford Textbook of Medicine. Editors Warell, D., Cox, T., Firth, J. and Benz E. 2004, Oxford University Press: Oxford.
166. Haslam, R. *Brain Tumors in Children in Textbook of Pediatrics*. Editors Nelson, W., Behrman, R., Kliegman, R. and Arvin, A. 1996, Harcourt Brace and Company: Philadelphia.
167. Abu-Arafeh, I. and Macleod, S. *Serious neurological disorders in children with chronic headache*. Arch Dis Child, 2005. 90(9): p. 937-940.
168. Dobrovoljac, M. et al. *Delay in the diagnosis of paediatric brain tumours*. European Journal of Pediatrics, 2002. 161(12): p. 663-7.

169. Flores, L.E. et al. *Delay in the diagnosis of pediatric brain tumors*. American Journal of Diseases of Children, 1986. 140(7): p. 684-6
170. Diamond, G. Chapter 73, Esotropia in Ophthalmology. Editors Yanoff M. and Duker, J.S. 2004, Moseby.
171. Diamond, G.R. Chapter 74, Exotropia, in Ophthalmology. Editors Yanoff M. and Duker, J.S. 2004, Moseby.
172. Bardoff, C. (2006) Acquired nystagmus. eMedicine
www.emedicine.com/oph/topic336.html
173. Sindhu, K. et al. *Aetiology of childhood proptosis*. Journal of Paediatrics and Child Health, 1998. 34(4): p. 374-376.
174. Rubin, S.E. Chapter 77, *Paralytic Strabismus in Ophthalmology*. Editors Yanoff M. and Duker, J.S. 2004, Moseby.
175. Digeorge, A. and Garibaldi L. *Disorders of pubertal development* in Nelson Textbook of Pediatrics. Editors Nelson, W., Behrman, R., Kliegman, R. and Arvin. 1996, Harcourt Brace and Company: Philadelphia.

APPENDIX 1 Summary of Recommendations

The quick reference and complete versions of the final guideline are shown below. The quick reference guideline presents the guideline statements whilst the complete guideline explains the rationale for each statement, its evidence level, subsequent recommendation grade and, where appropriate, the degree of consensus.

The diagnosis of brain tumours in children – an evidenced based guideline to assist healthcare professionals in the assessment of children presenting with symptoms and signs that may be due to a brain tumour (quick reference guide).

Statements in a **red box** advise on indications for imaging.

Statements in a **black box** advise on presentations frequently associated with misdiagnosis.

A one-page quick reference summary is shown in Figure 9.

1 Best practice

1a: Consultation

- Parents and their carers should be asked explicitly about their concerns in any consultation.
- If a parent/carer expresses concerns about a brain tumour or symptoms attributable to a brain tumour this should be reviewed carefully. If a brain tumour is unlikely the reason why should be explained with reference to the symptom card/decision support tool and appropriate safety netting advice given.
- If a child warrants a review, the timing of this review should comply with national diagnosis of all cancers (currently, diagnosis or all clear should be given to the patient within 4 weeks).
- If the patient, parent / carer and healthcare professional are not fluent in a common language an interpreter must be used for the consultation (www.language.co.uk).
- Low parental educational level, social deprivation and lack of familiarity with the UK healthcare system may be associated with diagnostic delay. Care must be taken for appropriate safety netting with a multi-disciplinary approach for these families (for example health visitor liaison).

1b: Referral

- A primary healthcare professional who has a high index of suspicion regarding a possible brain tumour should discuss their concerns with a secondary health care professional the same day.
- A child referred from primary care in which the differential diagnosis includes a possible space-occupying lesion should be seen in a rapid-access clinic or similar service (i.e. within 2 weeks)

1c: Imaging

- A child in whom CNS imaging is required to exclude a brain tumour (potential diagnosis but low index of suspicion) should be imaged and reported within 4 weeks to meet Department of health recommendations.
- MRI is the imaging modality of choice for a child who may have a brain tumour.
- If MRI is not available a contrast enhanced CT should be performed.
- Imaging results should be interpreted by a professional with expertise and training in central nervous system MR and CT imaging in children.
- The need to sedate or anaesthetise a child for imaging should not delay diagnosis and should be compliant with Department of Health guidance.

2. Predisposing factors

- Some predisposing factors (personal or family history of brain tumour, leukaemia, sarcoma and early onset breast cancer; prior therapeutic CNS radiation; NF1/2; tuberous sclerosis) are associated with an increased risk of childhood brain tumours. Patients/parents should be specifically asked about these factors in consultation as their presence may lower the threshold for referral and investigation.

3. Presentation and assessment of a child with a potential brain tumour

3a: Presenting symptoms and signs

The following symptoms and signs are all associated with childhood brain tumours. Their presence should alert the clinician to this possibility.

- Headache
- Nausea and / or vomiting
- Increasing head circumference(crossing centiles)
- Visual symptoms and signs including
 - Reduced visual acuity
 - Reduced visual fields
 - Abnormal eye movements
 - Abnormal fundoscopy
- Motor symptoms and signs including
 - Abnormal gait
 - Abnormal co-ordination
 - Focal motor abnormalities
- Growth and endocrine abnormalities including
 - Growth failure
 - Delayed, arrested or precocious puberty
 - Galactorrhoea

- Primary/secondary amenorrhoea
- Behavioural change
 - New onset mood disturbance
 - New onset pervasive lethargy
 - New onset withdrawal
 - New onset disinhibition
- Diabetes insipidus
- Seizures (see <https://www.nice.org.uk/guidance/qs27>)
- Altered consciousness (see <http://www.rcpch.ac.uk/system/files/protected/page/Decon%20guidelines.pdf>)

Symptoms and signs in childhood brain tumours may occur singularly or in combination.

3b: History

- Take detailed history and enquire specifically about:
 - Other symptoms (as listed above)
 - Predisposing factors
 - Family history

3c: Assessment

- Assess:
 - Visual system
 - Motor system
 - Height and weight
 - Head circumference if under 2 years
 - Pubertal status
- The initial symptoms of a brain tumour frequently mimic those that occur with many common childhood conditions
- Symptoms frequently fluctuate in severity – resolution and then recurrence does not exclude a brain tumour
- Presentation depends upon the age of the child
- A normal neurological examination does not exclude a brain tumour

It is important to note that due to the non-specificity of the symptoms, some children may be referred to sub-specialty doctors. A detailed history and assessment is required in these children

if the cause of the symptoms is not clear. Figure 2 shows the symptoms and signs in relation to the system/specialty.

4. Signs and Symptoms of a child with a potential brain tumour

4a: Headache

- Headache is a common symptom and is very rarely, in isolation, due to a brain tumour.
- Any child presenting with a headache should be assessed carefully for the other symptoms of a brain tumour, as listed in the presenting symptoms section of this guideline.
- A child with a headache without a clear cause requires careful review, the timing of which needs to be mindful of the differential diagnoses.
- Brain tumour headaches can occur at any time of the day or night
- Children aged younger than 4 years, or those with communication difficulties, are frequently unable to describe headache; their behaviour e.g. withdrawal, holding head may indicate a headache.
- In a child with a known migraine or tension headache a change in the nature of the headache requires reassessment and review of the diagnosis.

For more information regarding headaches there is a NICE guideline called “Headaches in over 12s: diagnosis and management”

<https://www.nice.org.uk/guidance/cg150/chapter/recommendations>

- Delayed diagnosis has been associated with failure to reassess a child with migraine or tension headache when the headache character changes.

CNS IMAGING REQUIRED FOR:

- Persistent headaches that wake a child from sleep
- Persistent headaches that occur on waking
- A persistent headache occurring at any time in a child younger than 4 years
- Confusion or disorientation occurring with a headache

Persistent headache with one or more other symptoms/signs associated with a brain tumour (i.e. nausea/vomiting, visual symptoms, increasing head circumference, motor symptoms, growth and endocrine symptoms, behavioural change)

4b: Nausea and vomiting

- Early specialist referral for consideration of underlying causes including CNS causes is required for a child with persistent nausea and / or vomiting. (Nausea and / or vomiting that lasts for more than two weeks should be regarded as persistent)
- Babies and young children under the age of 2 who may not be able to communicate other symptoms of raised intracranial pressure should have their head circumference measured, plotted and compared with previous measurements.

Delayed diagnosis has been associated with:

- Attributing persistent nausea and vomiting to an infective cause in the absence of corroborative findings e.g. contact with similar illness, pyrexia, diarrhoea.

CNS IMAGING REQUIRED FOR:

- Persistent vomiting on awakening (either in the morning or from a day time sleep)
NB: exclude pregnancy where appropriate.
- Persistent nausea and/or vomiting with 1 or more other symptoms/signs associated with a brain tumour (i.e. headache, visual symptoms, increasing head circumference, motor symptoms, growth and endocrine abnormalities, behavioural change) require CNS imaging.

4c Head Circumference

- A rapidly increasing head circumference (crossing centiles) can be a sign of an underlying brain tumour and requires referral to secondary care.
- In all babies with an increasing head circumference (crossing centiles), careful assessment of other symptoms of signs associated with a brain tumour should be undertaken.
- In babies in whom a head circumference is crossing centiles and a brain tumour is suspected an MRI is the imaging modality of choice within the appropriate timescale.

Delayed diagnosis has been associated with:

- Failure to measure head circumference in babies with unexplained persistent vomiting.

CNS IMAGING REQUIRED FOR:

- A rapidly increasing head circumference crossing centiles
- An increasing head circumference with 1 or more other symptoms/signs associated with a brain tumour (i.e. headache, nausea/vomiting, visual symptoms, motor symptoms, endocrine or growth symptoms, behavioural change) require CNS imaging.

4d: Visual symptoms and signs

- Consider a brain tumour in any child presenting with a persisting visual abnormality. (Any visual abnormality lasting longer than 2 weeks should be regarded as persistent)
- Parental / carer concern alone (including nursery staff) regarding a baby or young child's vision should be taken seriously and a referral for visual assessment should be made.
- Visual assessment must include assessment of:
 - Pupil responses
 - Visual fields in school age children
 - Eye movements
 - Optic disc appearance
 - Visual acuity
- If the assessing healthcare professional is unable to perform a complete visual assessment the child should be referred for assessment.
- Children referred for visual assessment with symptoms or signs suggestive of a brain tumour should be seen in a rapid access clinic or similar service (i.e. within 2 weeks).
- Community optometry should refer any child with abnormal eye findings suggestive of a possible brain tumour directly to secondary care.
- Consideration should be given to the appropriate place of assessment. If appropriate community optometry expertise is not available, pre-school and uncooperative children should be assessed by the hospital eye service.
- A child with a new onset non-paralytic (concomitant) squint should have early ophthalmological assessment for consideration of underlying causes (including CNS causes).

Delayed diagnosis has been associated with:

- Failure to fully assess vision in a young or uncooperative child
- Failure of communication between community optometry and primary and secondary care

CNS IMAGING REQUIRED FOR:

- Papilloedema
- Optic atrophy
- New onset nystagmus
- Reduction in visual acuity not attributable to an ocular cause
- Visual field reduction not attributable to an ocular cause
- Proptosis
- New onset paralytic (non-concomitant) squint
- Visual abnormality with 1 or more other symptoms/signs associated with a brain tumour (i.e. headache, nausea/vomiting, increasing head circumference, motor symptoms, growth and endocrine abnormalities, behavioural change) require CNS imaging.

4e: Motor symptoms and signs

- Consider a brain tumour in any child presenting with a persisting motor abnormality. (Any motor abnormality lasting longer than two weeks should be regarded as persistent.)
- A history of a change or deterioration in motor skills may indicate a brain tumour e.g. change in hand or foot preference, developmental regression, changes in gait, difficulties with balance.
- History should enquire into subtle changes in motor skills e.g. loss of learned skills (computer games, sport, handwriting).
- Assessment of a child's fine motor and visual-motor skills should include questioning or observation of:
 - handling of small objects e.g. cup, spoon, small toy
 - handwriting in older children.

Delayed diagnosis has been associated with:

- Attributing abnormal balance or gait to middle ear disease in the absence of corroborative findings
- Failure to identify swallowing difficulties as the cause of recurrent chest infections or "chestiness"

CNS IMAGING REQUIRED FOR:

Any child with focal neurological signs, for example:

- regression in motor skills
- abnormal gait or co-ordination unless attributable to a non-neurological cause
- focal motor weakness
- swallowing difficulties, without a local cause
- abnormal head position, without a local cause
- A motor abnormality with 1 or more other symptoms/signs associated with a brain tumour (i.e. headache, nausea/vomiting, visual symptoms, increasing head circumference, growth and endocrine abnormalities, behavioural change) require CNS

4f: Growth and endocrine

- Consider a brain tumour in any child presenting with any two of the following:
 - Growth failure
 - Delayed or arrested puberty
 - Polyuria and polydipsia
 - Galactorrhoea
 - Primary/secondary amenorrhoea

- If the history raises any concern, including parental concern, about any aspect of growth, the child's height, weight and head circumference (if under 2 years of age) should be measured and plotted on a growth chart.
- A child with a height or weight outside the normal range (<0.4th or >99.8th centiles, crossing centiles due to increased or decreased velocity outside that expected for age/pubertal stage or parental target range) should be referred to secondary care for assessment of their growth (see centile charts).
- Brain tumours can present with rapid weight loss or faltering growth, however the differential diagnosis when presented with this symptom is wide. If a young person presents with rapid weight loss, the other signs and symptoms of a brain tumour should be specifically looked for as part of the assessment.
- Early referral to secondary care is required for children presenting with precocious puberty, delayed or arrested puberty, growth failure, galactorrhoea, primary/secondary amenorrhoea or polyuria/polydipsia.
- Tumours affecting the midline supratentorial part of the brain can also affect vision. Children presenting with the above symptoms require a full visual assessment.

Delayed diagnosis has been associated with:

- Attributing impaired growth with vomiting to gastrointestinal disease in the absence of corroborative findings.
- Failure to consider diabetes insipidus in children with polyuria and polydipsia
- Failure to consider a brain tumour in young people with symptoms suggestive of an eating disorder
- Failure to assess vision in children presenting with these symptoms

CNS IMAGING REQUIRED FOR:

- An endocrine or growth abnormality with 1 or more other symptoms/signs associated with a brain tumour (i.e. headache, nausea/vomiting, visual symptoms, motor symptoms, increasing head circumference, behavioural change) require CNS imaging.

4g: Behaviour

- Brain tumours can manifest with neuropsychiatric symptoms including new onset mood disturbance, withdrawal, disinhibition and pervasive lethargy. If a child or young person presents with these symptoms, the other signs and symptoms of a brain tumour should be specifically looked for as part of the assessment.

- Environmental context is important when assessing lethargy: a child who is lethargic in situations in which they are normally active requires further assessment.

Delayed diagnosis has been associated with:

- Attributing behavioural change to “normal adolescent behaviour”
- Attributing mood disturbances to a psychiatric cause without full physical assessment.

THE DIAGNOSIS OF BRAIN TUMOURS IN CHILDREN: A GUIDELINE FOR HEALTHCARE PROFESSIONALS

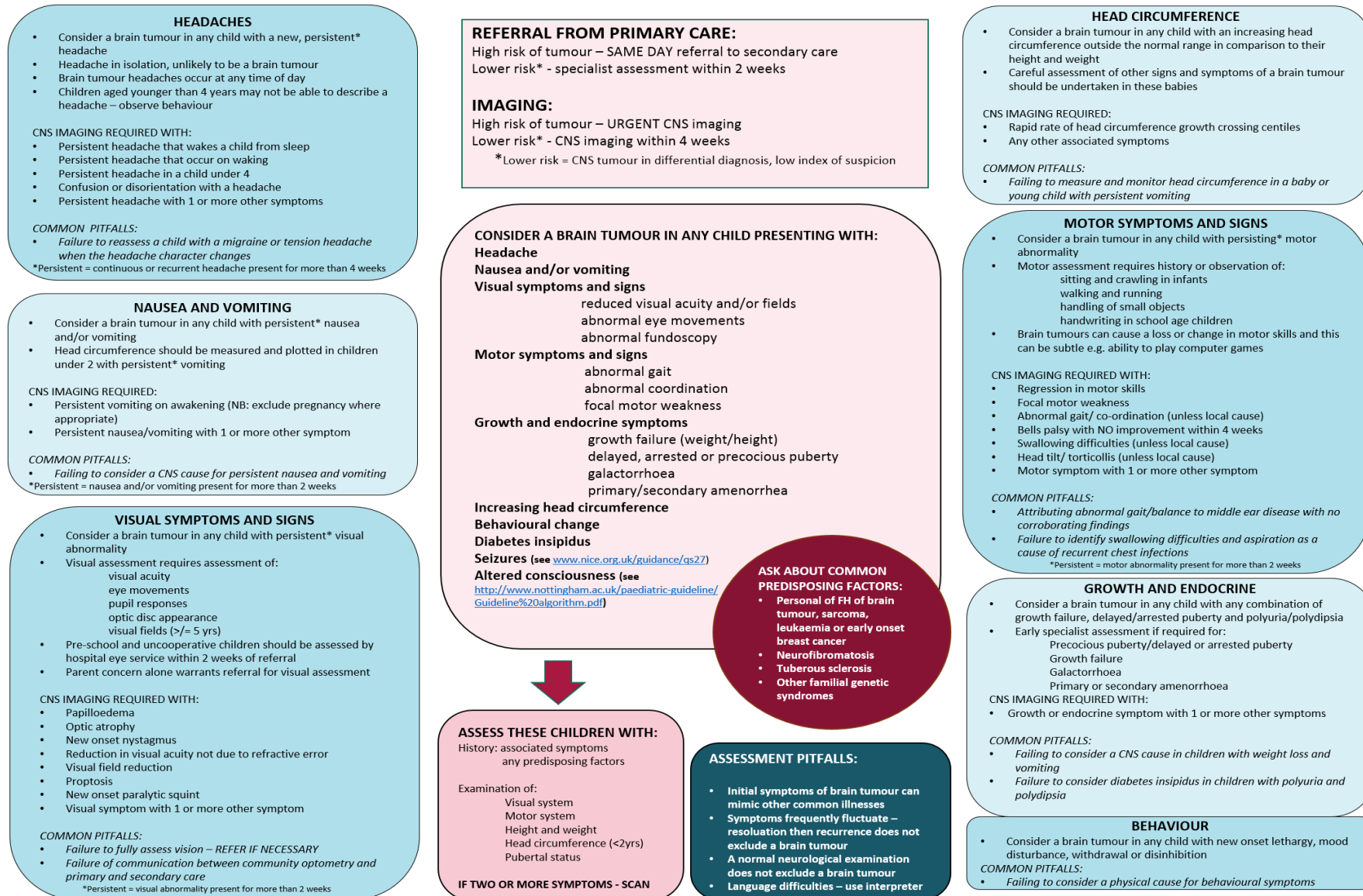


Figure 9 Quick reference guide

PRESENTING SYMPTOMS OF BRAIN TUMOURS BY SUB-SPECIALTY

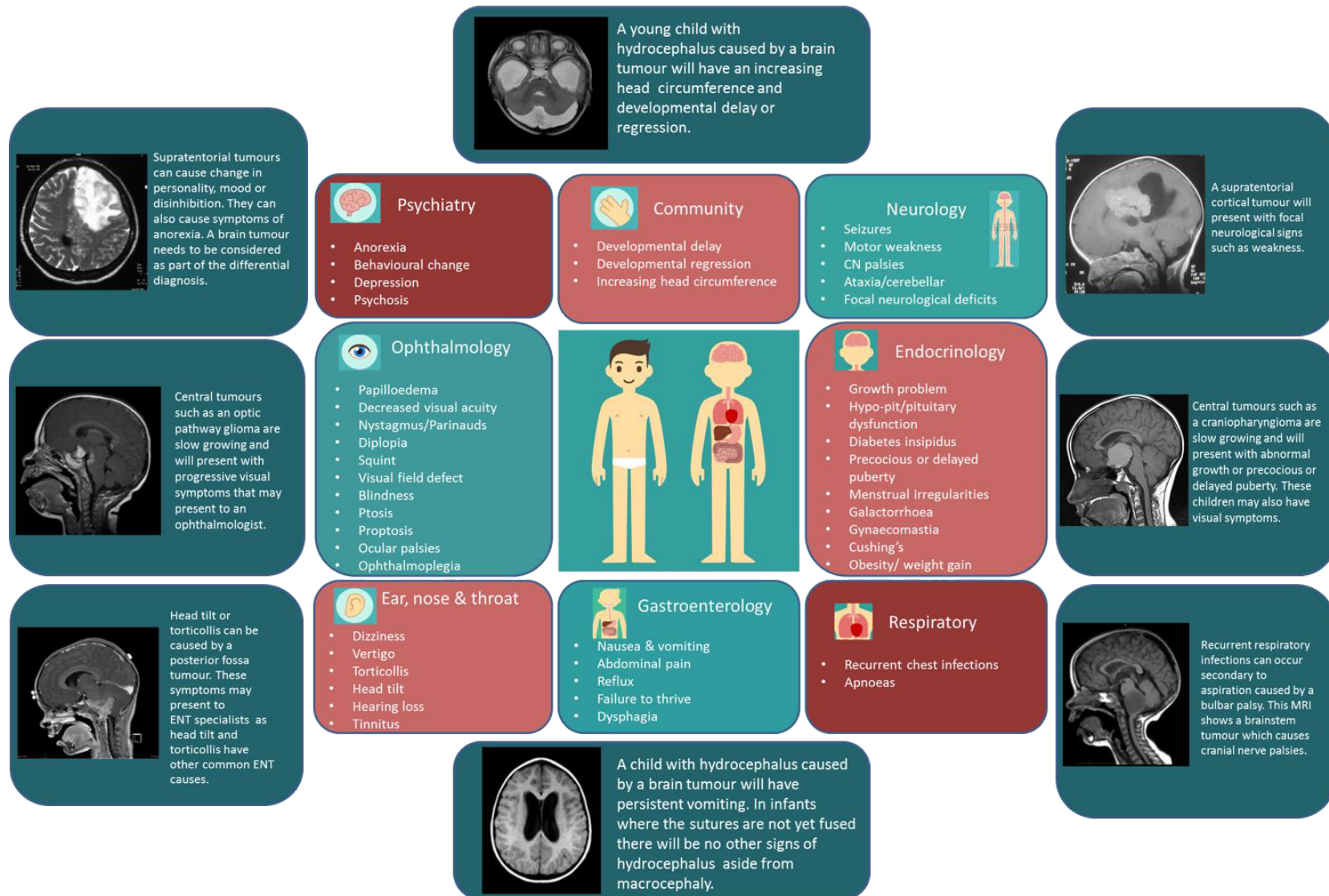


Figure 10. Brain tumour presentation by specialty

APPENDIX 2 Guideline summary for parents and young people

Any child or young person with symptoms that are unusual for him or her, or are persistent or unexplained, should be seen by a GP. If you are worried make an appointment with your doctor.

Please remember any child or young person needing urgent medical help should be taken to the nearest emergency department or dial 999.

A quarter of childhood cancers occur in the brain.

Early diagnosis of brain tumours can improve the outcome.

If you are worried you/your child has a brain tumour, tell your doctor

The HeadSmart Campaign is run by a partnership between the Children's Brain Tumour Research Centre (CBTRC) at The University of Nottingham, The Brain Tumour Charity and the Royal College of Paediatrics and Child Health (RCPCH).

It is funded and promoted by The Brain Tumour Charity.

If you would like to talk to someone about brain tumours, or the HeadSmart campaign, please contact the Support & Info Line at The Brain Tumour Charity on:

Freephone
0808 800 0004
or email
info@headsmart.org.uk

CBTRC Charitable Status Inland Revenue Number: X15294
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(England and Wales) SC045081 (Scotland) RCPCH Registered
Charity no: 1057744 © 2016 CBTRC, The University of
Nottingham, The Brain Tumour Charity and RCPCH. V3

HEAD SMART

**EARLY DIAGNOSIS
OF BRAIN TUMOURS**

symptoms card

This card is designed to help you know and spot the signs and symptoms of brain tumours in children and young people

BABIES

Symptoms include:

-  Persistent/recurrent vomiting
-  Balance/co-ordination /walking problems
-  Abnormal eye movements or suspected loss of vision
-  Behaviour change, particularly lethargy
-  Fits or seizures (not with a fever)
-  Abnormal head position such as wry neck, head tilt or stiff neck
-  Increasing head circumference (crossing centiles)

If your child has one of these, see your doctor, if two or more, ask for an 'urgent referral' 

CHILDREN

Symptoms include:


-  Persistent/recurrent headache
-  Persistent/recurrent vomiting
-  Balance/co-ordination /walking problems
-  Abnormal eye movements
-  Blurred or double vision / loss of vision
-  Behaviour change
-  Fits or seizures
-  Abnormal head position such as wry neck, head tilt or stiff neck

If your child has one of these, see your doctor, if two or more, ask for an 'urgent referral' 

TEENS

Symptoms include:

-  Persistent/recurrent headache
-  Persistent/recurrent vomiting
-  Balance/co-ordination /walking problems
-  Abnormal eye movements
-  Blurred or double vision / loss of vision
-  Behaviour change
-  Fits or seizures
-  Delayed or arrested puberty

If you or your child has one of these, see your doctor, if two or more, ask for an 'urgent referral' 

APPENDIX 3 GDG members, multidisciplinary workshop and Delphi participants

GDG Members

Professor David Walker, Professor of Paediatric Oncology, Children's Brain Tumour Research Centre, University of Nottingham, Nottingham, UK.

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Dr Sophie Wilne, Consultant Paediatric Oncologist, Nottingham Children's Hospital, Nottingham University Hospitals NHS Trust, Nottingham, UK.

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Jo-Fen Liu, Project Manager and Statistician, Children's Brain Tumour Research Centre, University of Nottingham, UK.

Multidisciplinary Workshop Participants

Mrs Pam White, Parent representative, Notts.

Mrs Louise Whittle, PASIC Treasurer and parent representative, QMC, Nottingham

Dr Rebecca Sands, Consultant Paediatrician, Kings Mill Hospital

Dr Carol Bertenshaw, Consultant Paediatrician, QMC, Nottingham

Dr Lynda Walton, Consultant Paediatric Emergency, QMC, Nottingham

Dr Rob Dineen, Consultant Neuroradiologist, QMC, Nottingham.

Dr Julie Mott, Consultant Emergency Paediatrician, Royal Derby Hospital, Derby.

Dr Louise Denvir, Consultant Paediatric Endocrinologist, QMC, Nottingham

Dr Manish Prasad, Consultant Paediatric Neurologist, QMC, Nottingham.

Dr Paul Nathan, General Practitioner, Derby

Dr Rebecca Chellaswamy, General Practitioner, Derby

Dr Vicki Lee, Consultant in Paediatric Oncology, Sheffield Children's Hospital

Research Team

Dr Shaarna Shanmugavadivel, Clinical Education Fellow, University of Nottingham

Ms Jo-Fen Liu, HeadSmart Project Manager, University of Nottingham.

Dr Sophie Wilne, Consultant in Paediatric Oncology, Nottingham Children's Hospital

Professor David Walker, Professor of Paediatric Oncology, University of Nottingham

Delphi Consensus Participants

Name	Occupation
Mr D Macarthur	Consultant Neurosurgeon, QMC, Nottingham
Dr C Dunkley	Consultant Paediatrician, King's Mill Hospital, Mansfield
Dr A Sequeira	General Practitioner, London
Dr C Bosman	Consultant Paediatrician, Lincoln County Hospital
Dr C Brown	Consultant Paediatrician, QMC, Nottingham
Dr C Rittey	Consultant Paediatric Neurologist, Sheffield
Dr A Jenkins	Consultant Paediatric Oncologist, Sheffield
Dr S Smith	Consultant Emergency Paediatrician, QMC, Nottingham
Dr I Heyman	Consultant in CAMHS, Great Ormond Street
Dr T Randell	Consultant Paediatric Endocrinologist, QMC, Nottingham
Dr A Langham	General Practitioner, Manchester
Dr T Tinklin	Consultant Paediatrician and Endocrinologist, Derby
Dr L Wells	Consultant Paediatrician, QMC, Nottingham
Dr M Brougham	Consultant Paediatric Oncologist, Edinburgh
Dr M Yanney	Consultant Paediatrician, King's Mill Hospital, Mansfield
Dr C Chaney	General Practitioner, Belper
Dr A McCarthy	Consultant Paediatric Oncologist, Belfast
Dr G Chow	Consultant Paediatric Neurologist, QMC, Nottingham
Dr L Hudson	Consultant Paediatrician, Great Ormond Street
Dr A Soman	Consultant Paediatrician, Norfolk
Dr H Clements	Consultant Paediatrician, KMH, Mansfield
Dr B Subramaniam	Consultant Neonatologist, Derby
Dr J-P Kilday	Consultant in Paediatric Oncology, Manchester
Dr J Surridge	Consultant Emergency Paediatrician, Derby
Dr E Williams	General Practitioner, Coventry
Dr J Ellis	Consultant Paediatrician, KMH, Mansfield
Dr I Lewins	Consultant Emergency Paediatrician, Derby
Dr J McIntyre	Consultant Neonatologist, Derby
Dr B Pizer	Consultant Paediatric Oncologist, Liverpool
Dr M English	Consultant Paediatric Oncologist, Birmingham
Dr A Maronge	General Practitioner, Belper
Dr P Dykes	Consultant Emergency Paediatrician, QMC, Derby
Dr U Ngwu	Consultant Paediatrician, KMH, Mansfield
Dr K Tallur	Consultant Paediatric Neurologist, Edinburgh
Dr H Sammons	Consultant Paediatrician, Derby
Dr W Carroll	Consultant Paediatrician (respiratory), Stoke
Dr C Posner	General Practitioner, Belper
Dr S Gibbs	Consultant Emergency Paediatrician, Sheffield
Dr I Saeed	General Practitioner, Coventry
Dr C Dieppe	Consultant Emergency Paediatrician, QMC, Nottingham
Dr J Sussens	Consultant Paediatrician, QMC, Nottingham
Dr M Stark	Consultant Paediatrician, Edinburgh
Dr V Cox	Consultant Paediatrician, Derby
Dr E Marder	Consultant Community Paediatrician, Nottingham

Dr N Aswani	Consultant Paediatrician and Endocrinologist, Derby
Dr M Hewitt	Consultant Paediatric Oncologist
Dr D Traves	Consultant Paediatrician, Derby
Dr S Rathi	Consultant Paediatrician, KMH, Mansfield
Dr D Nathan	Consultant Community Paediatrician, Nottingham
Dr S Rhodes	Consultant Paediatrician, KMH, Mansfield
Dr J-A Maney	Consultant Emergency Paediatrician, Belfast
Dr S Bailey	Consultant Paediatric Oncologist, Newcastle Upon Tyne
Dr R Hoenderkamp	General Practitioner, London
Dr N Ruggins	Consultant Neonatologist, Derby
Dr N Shah	Consultant Paediatric gastroenterologist, GOSH
Dr T Wolff	Consultant Community Paediatrician, Nottingham
Dr C Nahman	Consultant CAHMS, Nottingham

Further Acknowledgment

Dr D Wood, Consultant Paediatrician at Nottingham Children's Hospital for their expertise and guidance in areas of the guideline concerning young people and adolescents.

APPENDIX 4 Conflicts of interest policy

CHILDREN'S BRAIN TUMOUR RESEARCH CENTRE POLICY ON CONFLICTS OF INTEREST

Introduction

The Children's Brain tumour Research Centre (CBTRC) as part of the University of Nottingham is expected to achieve high standards of probity, including integrity and objectivity, especially when managing public funds. Managing conflicts of interest is an important part of this process.

Overall, the CBTRC requires that all members of the Guideline Development Group declare their interests in a transparent way and that this information is publically available.

Scope of the Policy

Who is covered?

This policy applies to the

- Guideline development group chair and members
- Expert advisors (e.g. participants of a workshop or Delphi consensus process)

It is important to note that the Chair of the Guideline Development Group cannot have any conflicts. Conflicts including those in the previous 12months of joining need to be declared.

What is a conflict of interest?

A conflict of interest occurs when the judgement of a member of the group may be compromised due to a financial or other interest detailed in the policy below.

A declared interest will need to undergo a consultation process as outlined in this policy to determine whether or not it is in conflict with the work being carried out.

It is important to note that if an individual is living with a disease or condition or has a family member who suffers from the disease, it is NOT regarded as a conflict of interest.

Types of interests

Interests can be specific or non-specific and financial or non-financial. Financial interests can be classified as personal or non-personal.

- *Specific*: if the interest is directly linked to the subject being discussed
- *Non-specific*: if the interest is not linked to the subject matter being discussed
- *Financial*: includes anything of monetary value (examples include payments for services, equity interests, stocks, intellectual property rights, royalties, patents)
- *Personal financial*: where the individual appears to have personal financial gain which could be to themselves or a member pf their family.
- *Non-personal financial*: involves payment or other benefit to the department or organisation but not personally.
- *Personal non-financial*: related to publications of opinions/research related to the subject matter under discussion.

How do we manage the conflicts declared?

All conflicts declared are discussed at the CBTRC board meeting. Below are the expected outcomes of each conflict:

- 1. Personal financial interests which are specific**
REFUSAL (in exceptional circumstances the chair may allow them to attend to answer certain questions)
- 2. Personal financial interested which are non-specific**
SIMPLE DECLARATION AND PARTICIPATION
- 3. Personal non-financial interests which are specific**
DECLARATION AND AWAIT DECISION – the chair must decide on whether participation appropriate
- 4. Personal non-financial interests which are non-specific**
SIMPLE DECLARATION AND PARTICIPATION
- 5. Non-financial interests which are specific**
SIMPLE DECLARATION AND PARTICIPATION
- 6. Non-financial personal interests which are non-specific#**
SIMPLE DECLARATION AND PARTICIPATION

Those interests which allow simple declaration and participation, can in exceptional circumstances be refused participation if the Chair feels on consulting with the Board that there is a conflict. Overall the majority of the guideline development group should not have conflicts.

How do we record interests?

A record is kept at the CBTRC of all declarations and minutes of meetings. They will be made publically available and listed on the guideline. All declarations are subject to disclosure under the Freedom of Information Act 2000.

APPENDIX 5 Multidisciplinary workshop conflict of interest forms (see attached PDF)

APPENDIX 6 Delphi consensus conflict of interest forms (see attached PDF)

APPENDIX 7: Literature review search terms and strategy

1. "brain tumour*" .ti.ab
2. "brain tumor*" .ti.ab
3. "brain neoplasm*" .ti.ab
4. exp BRAIN NEOPLASMS/
5. BRAIN NEOPLASMS/DI
6. "SPINAL CORD TUMOUR*" .ti.ab
7. "spinal cord tumour*" .ti.ab
8. "spinal cord neoplasm*" .ti.ab
9. exp SPINAL CORD NEOPLASMS/
10. SPINAL CORD NEOPLASMS/DI [DI=diagnosis]
11. diagnosis .ti.ab
12. exp DIAGNOSIS/
13. diagnosis* .ti.ab
14. sign* .ti.ab
15. symptom* .ti.ab
16. exp SIGNS AND SYMPTOMS/
17. (signs AND symptoms*) .ti.ab
18. presentation* .ti.ab
19. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
20. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
21. 19 AND 20
22. 21 [Limit to: Publication Year 2005-2015 and Abstract included and (Age group Infant, newborn or Infant or Child, preschool or Child or Adolescent or Young Adult) and Humans]

APPENDIX 8 Delphi consensus process results

Delphi process round one

Round one of the Delphi consensus process comprised of 30 statements describing the presenting features of childhood brain tumours, factors that could be used to discriminate brain tumours from other less serious conditions and possible referral pathways for children with brain tumours.

The Delphi consensus questionnaire was sent out electronically via email with the following message:

Dear All,

Thank you so much for agreeing to participate in this Delphi process. These statements have been devised by a multi-disciplinary team after detailed review of the current guideline and additional of new evidence from a recent systematic review and meta-analysis. This guideline is for use by both primary and secondary healthcare professionals.

This is round 1 and consists of 30 statements for you to rate between 1 and 9. There are comments boxes after each statement if there are particular amendments you would like to suggest.

In completing this process, your name will appear on the final guideline.

Best Wishes
Shaarna Shanmugavadivel
Clinical Oncology Education Fellow
Children's Brain Tumour Research Centre
Nottingham

137 clinicians were invited to take part in the Delphi process. 62 panel members returned the round one questionnaire within the required time frame. Statements were taken as having reached consensus if 75% or more of the Delphi panel respondents rated the statement 7, 8 or 9. Statements were rejected if 25% or less of the Delphi panel rated the statements 7, 8 or 9. Ratings of N/C, blanks or two boxes checked in error were excluded from the analysis of that statement. 24 of the 30 original statements reached consensus, none were rejected and the remaining 6 statements were modified or excluded based upon feedback.

The following statements from round one reached consensus:

- C1. If a parent/carer expressed concerns about a brain tumour this should be reviewed carefully. If a brain tumour is unlikely the reasons why should be explained by reference to the symptom card/decision support tool and appropriate safety netting advice given.
- C2. If a child warrants a review, the timing of this review should comply with national diagnosis of all cancers (currently, diagnosis or all clear should be given to the patient within 4 weeks).
- C3. Some predisposing factors (personal or family history of brain tumour, leukaemia, sarcoma and early onset breast cancer; prior therapeutic CNS

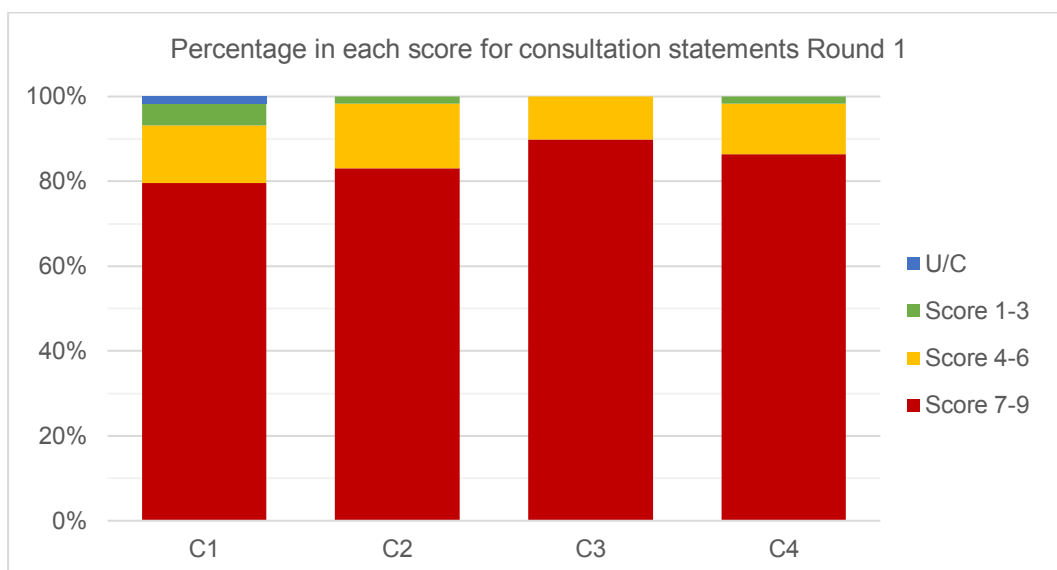
radiation; NF1/2; tuberous sclerosis) are associated with an increased risk of childhood brain tumours. Patients/parents should be specifically asked about these factors in consultation as their presence may lower the threshold for referral and investigation.

- C4. Low parental educational level, social deprivation and lack of familiarity with the UK healthcare system may be associated with diagnostic delay. Care must be taken for appropriate safety netting and multi-disciplinary approach in these families.
- R1. A child referred from primary care in which the differential diagnosis includes a possible space-occupying lesion should be seen in a rapid-access clinic or similar service (ie within 2 weeks)
- IM1. A child in whom CNS imaging is required to exclude a brain tumour (potential diagnosis but low index of suspicion) should be imaged and reported within 4 weeks to meet Department of health recommendations.
- IM2. The need to sedate or anaesthetise a child for imaging should not delay diagnosis and should be compliant with Department of Health guidance.
- H1. Headache is a common symptom and is very rarely, in isolation, due to a brain tumour.
- H2. Any child presenting with a headache should be assessed carefully for the other symptoms of a brain tumour, as listed in the guideline.
- H3. A child with headache without a clear cause requires careful review, the timing of which needs to be mindful of the differential diagnoses and national guidance.
- NV1. Persistent nausea and/or vomiting with 1 or more other symptoms/signs associated with a brain tumour (ie headache, visual symptoms, motor symptoms, growth and development abnormalities, behavioural change) require CNS imaging.
- NV2. Young children under the age of 2 who may not be able to communicate other symptoms of raised intracranial pressure should have their head circumference monitored.
- V1. Parental / carer concern alone (including nursery staff) regarding a baby or young child's vision should be taken seriously and a referral for visual assessment should be made.
- M1. A history of a change or deterioration in motor skills may indicate a brain tumour e.g. change in hand or foot preference, developmental regression
- M2. History should enquire into subtle changes in motor skills e.g. loss of learned skills (computer games, sport, handwriting)
- M3. Assessment of a child's fine motor and visual-motor skills should include questioning or observation of:
 - handling of small objects e.g. cup, spoon, small toy
 - handwriting in older children.
- M4. CNS imaging is required for any child with focal neurological signs, for example:
 - regression in motor skills
 - abnormal gait or co-ordination unless attributable to a non-neurological cause
 - focal motor weakness
 - swallowing difficulties (unless local cause)
 - abnormal head position

- GR2. A child with a height or weight outside the normal range (<0.4th or >99.8th centiles, crossing centiles due to increased or decreased velocity outside that expected for age/pubertal stage or parental target range) should be referred to secondary care for assessment of their growth (see centile charts).
- GR3. Early referral to secondary care is required for children presenting with precocious puberty, delayed or arrested puberty, growth failure (see GR2 for definition), galactorrhoea, primary/secondary amenorrhoea or polyuria/polydipsia.
- GR4. Tumours affecting the midline supratentorial part of the brain can also affect vision. In children presenting with the above symptoms in statement GR3 require a full visual assessment.
- B1. Brain tumours can manifest with neuro-psychiatric symptoms.
- B3. Children presenting with new onset mood disturbance, withdrawal and disinhibition require careful assessment looking for other signs and symptoms of a brain tumour.
- HC1. A rapidly increasing head circumference or macrocephaly can be a sign of an underlying brain tumour and requires referral to secondary care.
- HC2. A rapid increase of head circumference is defined as one that crosses 2 centiles on the head circumference growth chart.
- HC4. In all babies with an increasing head circumference, careful assessment of other symptoms of signs associated with a brain tumour should be undertaken.

RESULTS of ROUND ONE

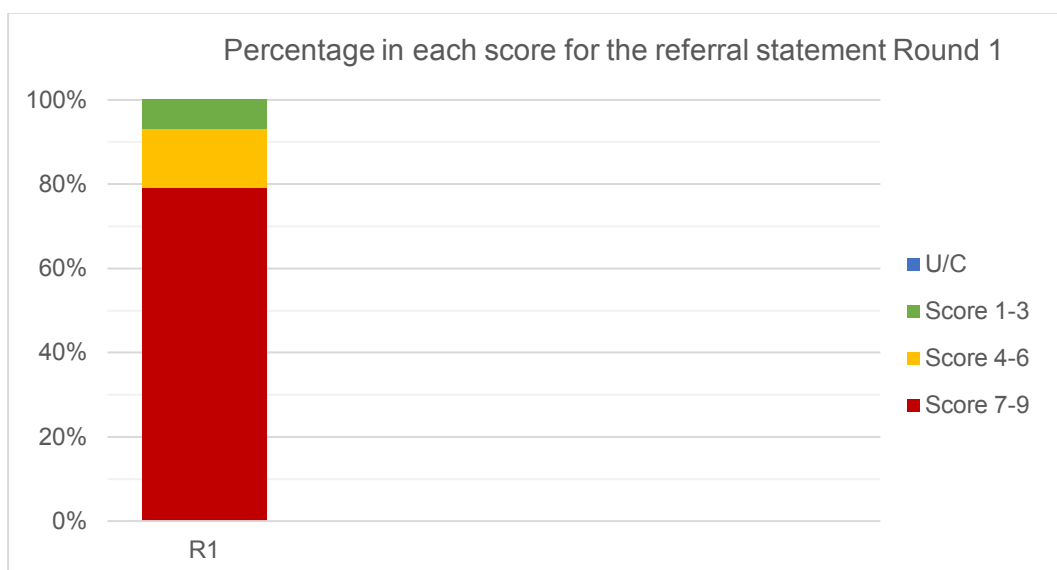
CONSULTATION STATEMENTS for Delphi Round 1:



All four CONSULTATION statements achieved consensus in Round One:

- C1.** If a parent/carer expressed concerns about a brain tumour this should be reviewed carefully. If a brain tumour is unlikely the reasons why should be explained by reference to the symptom card/decision support tool and appropriate safety netting advice given.
- C2.** If a child warrants a review, the timing of this review should comply with national diagnosis of all cancers (currently, diagnosis or all clear should be given to the patient within 4 weeks).
- C3.** Some predisposing factors (personal or family history of brain tumour, leukaemia, sarcoma and early onset breast cancer; prior therapeutic CNS radiation; NF1/2; tuberous sclerosis) are associated with an increased risk of childhood brain tumours. Patients/parents should be specifically asked about these factors in consultation as their presence may lower the threshold for referral and investigation.
- C4.** Low parental educational level, social deprivation and lack of familiarity with the UK healthcare system may be associated with diagnostic delay. Care must be taken for appropriate safety netting and multi-disciplinary approach in these families.

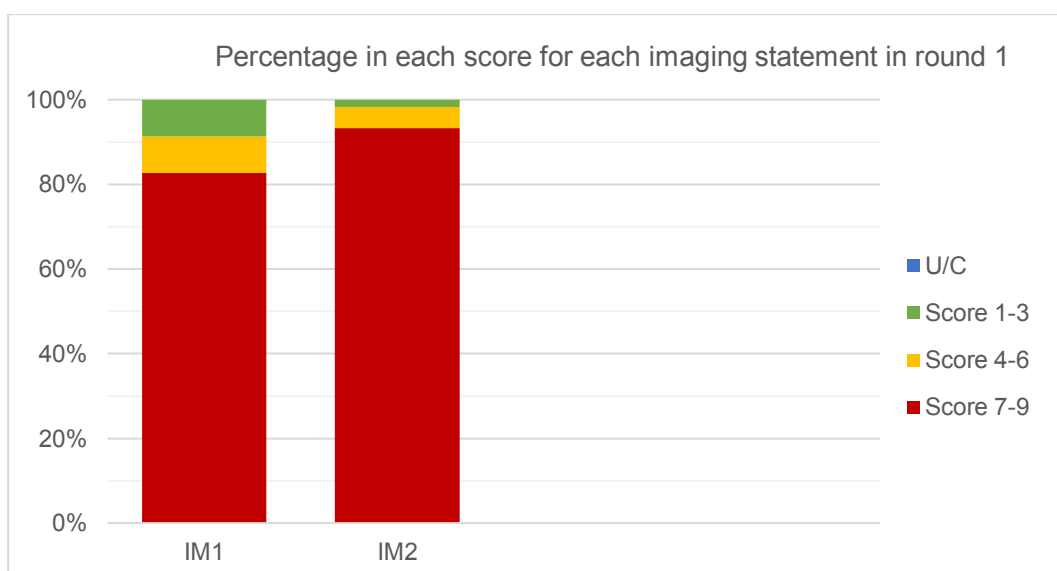
REFERRAL STATEMENTS for Delphi Round 1:



The one REFERRAL statement achieved consensus in Round One:

- R1.** A child referred from primary care in which the differential diagnosis includes a possible space-occupying lesion should be seen in a rapid-access clinic or similar service (i.e. within 2 weeks)

IMAGING STATEMENTS for Delphi Round 1:

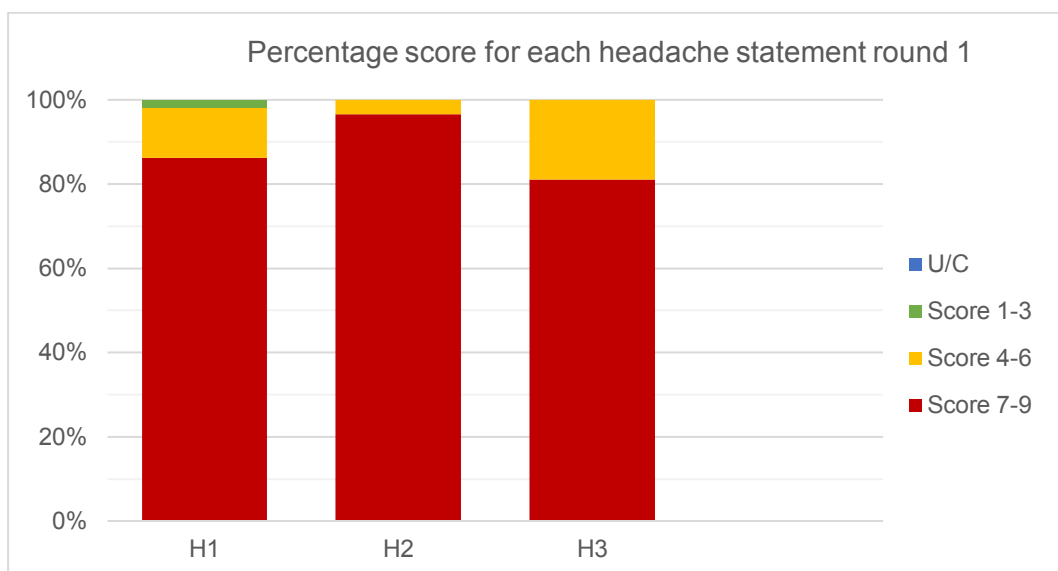


Both IMAGING statements achieved consensus in Round One:

- IM1.** A child in whom CNS imaging is required to exclude a brain tumour (potential diagnosis but low index of suspicion) should be imaged and reported within 4 weeks to meet Department of health recommendations.

- IM2.** The need to sedate or anaesthetise a child for imaging should not delay diagnosis and should be compliant with Department of Health guidance.

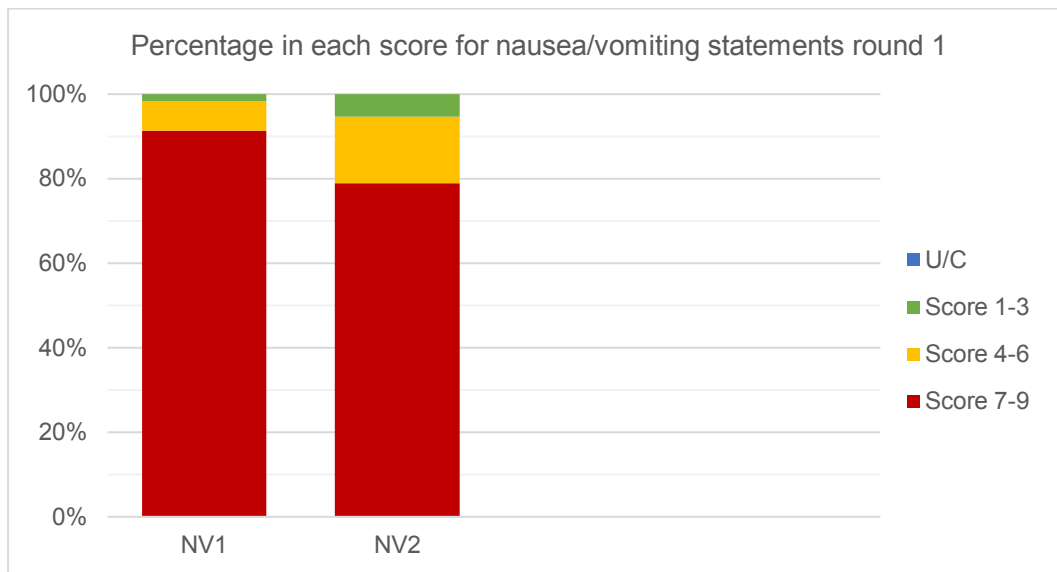
HEADACHE STATEMENTS for Delphi Round 1:



All three HEADACHE statements achieved consensus in Round One:

- H1.** Headache is a common symptom and is very rarely, in isolation, due to a brain tumour.
- H2.** If a Any child presenting with a headache should be assessed carefully for the other symptoms of a brain tumour, as listed in the guideline.
- H3.** A child with headache without a clear cause requires careful review, the timing of which needs to be mindful of the differential diagnoses and national guidance.

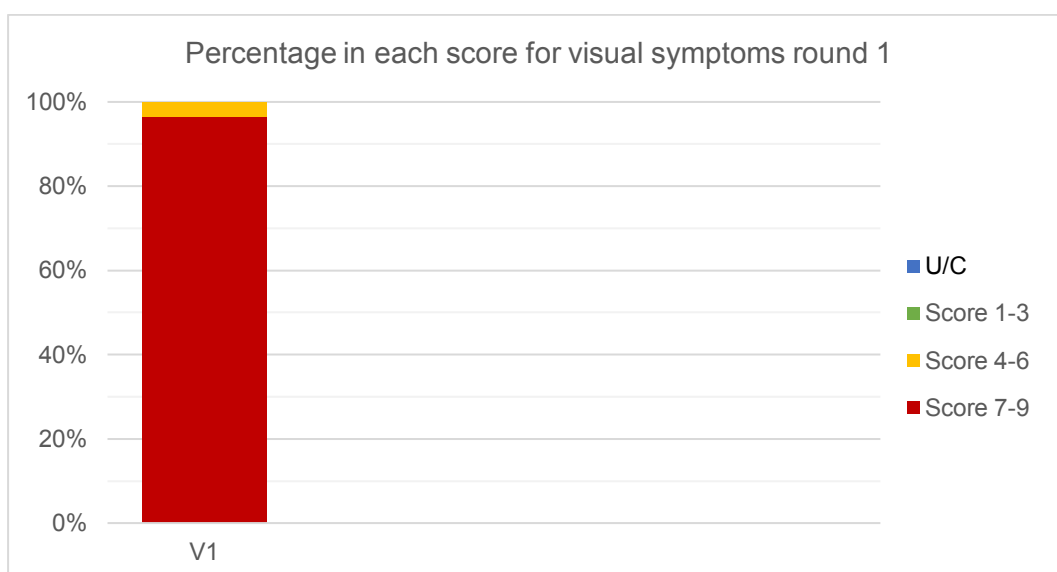
NAUSEA & VOMITING STATEMENTS for Delphi Round 1:



The following two NAUSEA & VOMITING statements achieved consensus in Round One:

- NV1.** Persistent nausea and/or vomiting with 1 or more other symptoms/signs associated with a brain tumour (ie headache, visual symptoms, motor symptoms, growth and development abnormalities, behavioural change) require CNS imaging.
- NV2.** Young children under the age of 2 who may not be able to communicate other symptoms of raised intracranial pressure should have their head circumference monitored.

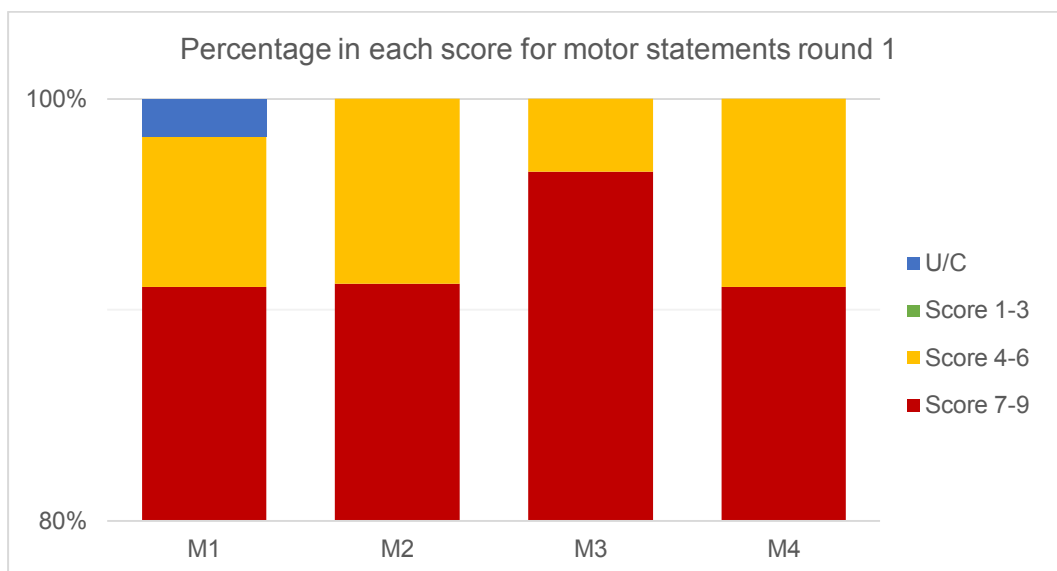
VISUAL SYSTEM STATEMENTS for Delphi Round 1:



The following VISUAL SYSTEM statement achieved consensus in Round One:

- V1.** Parental / carer concern alone (including nursery staff) regarding a baby or young child's vision should be taken seriously and a referral for visual assessment should be made.

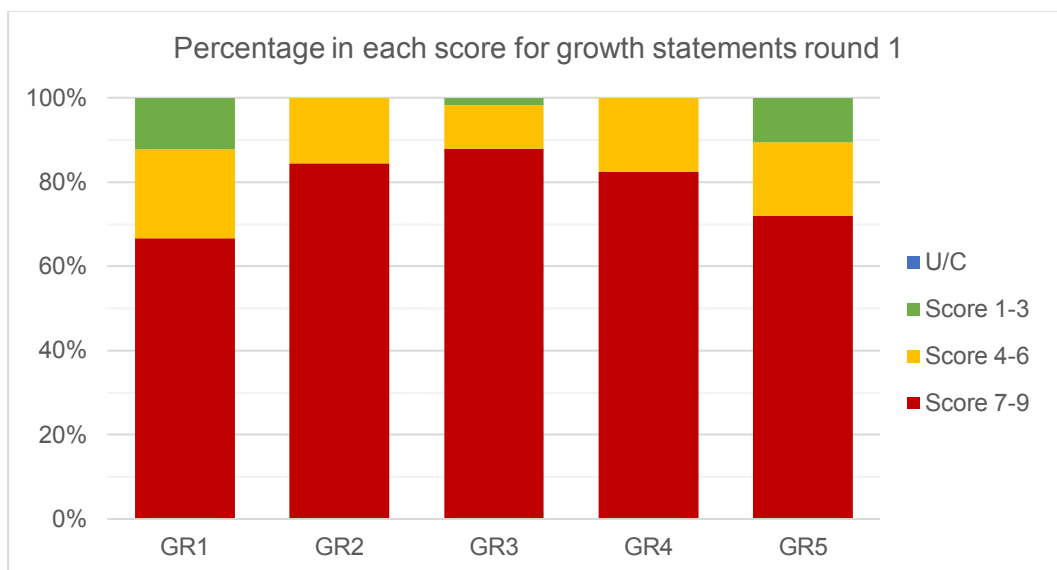
MOTOR SYSTEM STATEMENTS for Delphi Round 1:



The following four MOTOR SYSTEM statements achieved consensus in Round One:

- M1.** A history of a change or deterioration in motor skills may indicate a brain tumour e.g. change in hand or foot preference, developmental regression
- M2.** History should enquire into subtle changes in motor skills e.g. loss of learned skills (computer games, sport, handwriting)
- M3.** Assessment of a child's fine motor and visual-motor skills should include questioning or observation of:
- handling of small objects e.g. cup, spoon, small toy
 - handwriting in older children.
- M4.** CNS imaging is required for any child with focal neurological signs, for example:
- regression in motor skills
 - abnormal gait or co-ordination unless attributable to a non-neurological cause
 - focal motor weakness
 - swallowing difficulties (unless local cause)
 - abnormal head position

GROWTH STATEMENTS for Delphi Round 1:



The following three GROWTH SYSTEM statements achieved consensus in Round One:

- GR2.** A child with a height or weight outside the normal range (<0.4th or >99.8th centiles, crossing centiles due to increased or decreased velocity outside that expected for age/pubertal stage or parental target range) should be referred to secondary care for assessment of their growth (see centile charts).
- GR3.** Early referral to secondary care is required for children presenting with precocious puberty, delayed or arrested puberty, growth failure (see GR2 for definition), galactorrhoea, primary/secondary amenorrhoea or polyuria/polydipsia.
- GR4.** Tumours affecting the midline supratentorial part of the brain can also affect vision. In children presenting with the above symptoms in statement GR3 require a full visual assessment.

The following three GROWTH statements did NOT achieve consensus in Round One, and have been modified for voting in Round Two, or excluded.

GR1. Height and weight should be routinely measured and plotted on the appropriate growth chart for every child at every contact with a healthcare professional.

Outcome: Statement modified for Round 2, in light of comments received (appendix 9).

Reason: Feedback from the panel, in particular the primary healthcare professionals suggested this was not feasible. Modified as below.

GR5. If a young person presents with rapid weight loss/underweight, a careful assessment should be undertaken looking for the other signs and symptoms of a brain tumour. If none of these are present they should be referred for eating disorder assessment and care. Should there be any concerns about atypical clinical features the team should consult with a paediatrician

experienced in eating disorders care to determine if further investigation is required. This should not delay referral to the CAMHS team.

Outcome: Statement modified for Round 2, in light comments received (appendix 4).

Reason: On review, the comments highlighted that weight loss or growth faltering can have a wide differential diagnosis and the statement was amended as such.

MODIFIED GR1. If the history raises any concern, including parental concern about any aspect of growth, the child's height weight and head circumference (if under 2 years of age) should be measured and plotted on a growth chart.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree

N/C ☐

Comments:

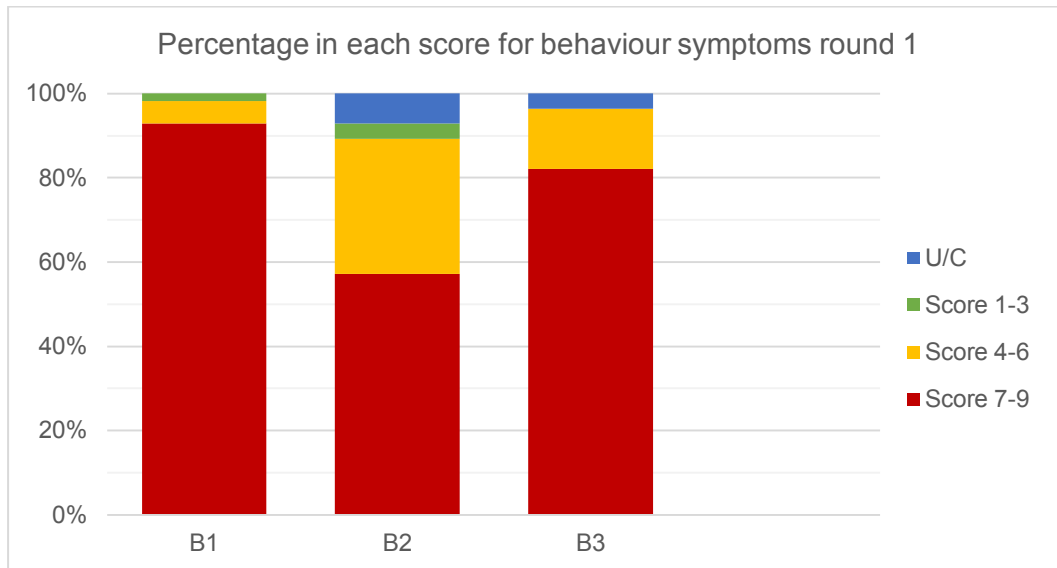
MODIFIED GR5. Brain tumours can present with rapid weight loss or faltering growth, however the differential diagnosis when presented with this symptom is wide. If a young person presents with rapid weight loss, the other signs and symptoms of a brain tumour should be specifically looked for as part of the assessment.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree

N/C ☐

Comments:

BEHAVIOUR SYMPTOMS STATEMENTS for Delphi Round 1:



The following two BEHAVIOUR SYMPTOMS statements achieved consensus in Round One:

- B1.** Brain tumours can manifest with neuro-psychiatric symptoms.
- B3.** Children presenting with new onset mood disturbance, withdrawal and disinhibition require careful assessment looking for other signs and symptoms of a brain tumour.

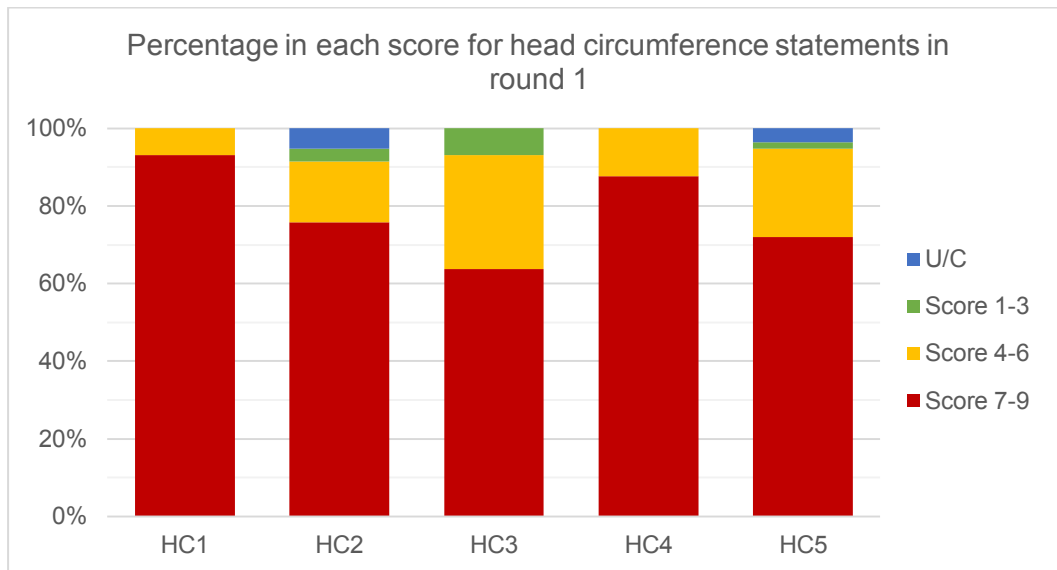
The following BEHAVIOUR SYMPTOMS statement did NOT achieve consensus in Round One, and has been excluded:

B2. Pervasive lethargy is an under-recognised symptom in brain tumours and warrants careful assessment of the other symptoms in order to make a diagnosis.

Outcome: Statement excluded.

Reason: B1 and B3 including lethargy was merged into one statement and sent out in round 2 as statement B2.

HEAD CIRCUMFERENCE STATEMENTS for Delphi Round 1:



The following three HEAD CIRCUMFERENCE statements achieved consensus in Round One:

- HC1.** A rapidly increasing head circumference or macrocephaly can be a sign of an underlying brain tumour and requires referral to secondary care.
- HC2.** A rapid increase of head circumference is defined as one that crosses 2 centiles on the head circumference growth chart.
- HC4.** In all babies with an increasing head circumference, careful assessment of other symptoms of signs associated with a brain tumour should be undertaken.

The following TWO HEAD CIRCUMFERENCE statements did NOT achieve consensus in Round One, and have been modified for voting in Round Two, or excluded.

HC3. If a healthcare professional has concerns that a baby has an increasing head circumference macrocephaly in relation to its height and weight, but has not crossed threshold for referral then provided the baby is otherwise asymptomatic 2 weekly monitoring of the head circumference is appropriate.

Outcome: Statement excluded.

Reason: On review, the guideline development group felt that this was too prescriptive and should be excluded.

HC5. For a baby whose head circumference has been correctly plotted and increased by 2 centile or more, an MRI is the imaging modality of choice within the appropriate timescale.

Outcome: This statement was modified and sent out in Round 2 Delphi.

MODIFIED HC. In babies in whom a head circumference is increasing and a brain tumour is suspected an MRI is the imaging modality of choice within the appropriate timescale.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree
N/C ☐
Comments:

Delphi questionnaire round two results

The statements for the second round of the Delphi consensus process were derived from the feedback of the first round.

Round two of the Delphi consensus process comprised of 4 statements describing the presenting features of childhood brain tumours, factors that could be used to discriminate brain tumours from other less serious conditions and possible referral pathways for children with brain tumours.

This round was sent, electronically, to all those who completed round one with the following message:

Dear All,

Thank you so much for participating in the first round of our Delphi consensus process, we really appreciate your expertise.

We have reached consensus on 24 out of 30 statements.

We have excluded 2 statements after further discussions within the multidisciplinary workshop group.

This second round contains FOUR STATEMENTS and should take around 5 minutes to complete. The deadline for submission is the 31st of August.

Once we have reached consensus on all the statements we will send out a letter outlining your participation and of course, your name will be included in the guideline.

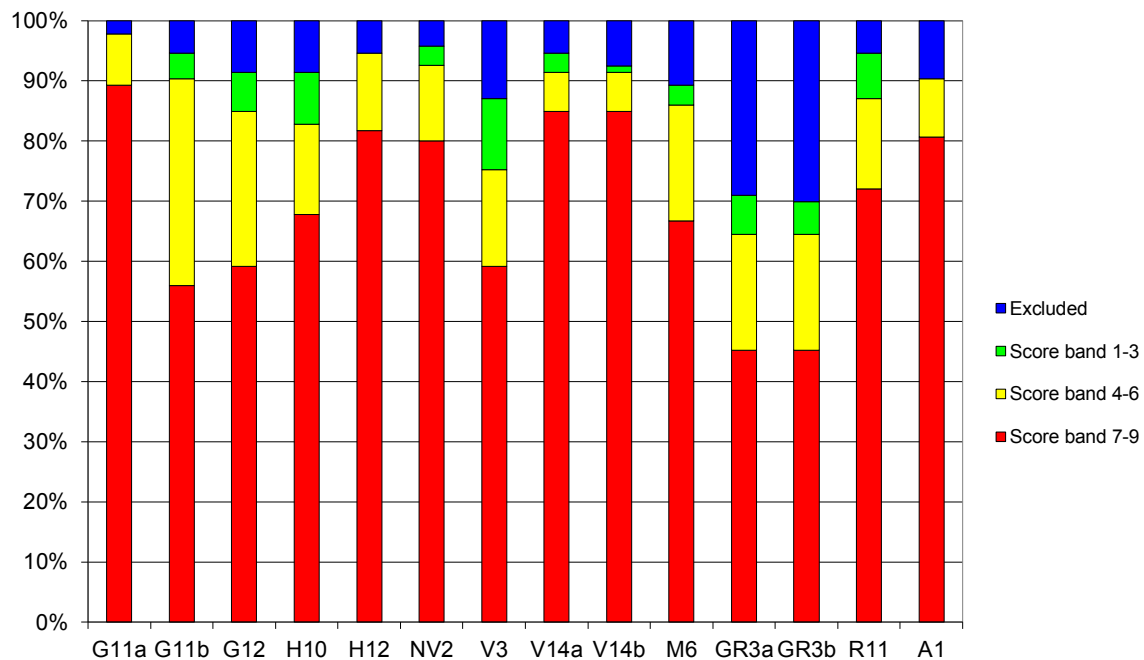
We thank you once again for your participation. Here is the link for round 2:
<https://www.surveymonkey.co.uk/r/HeadSmartDelphi2>

Best Wishes,

Round two was issued to the 62 participants returning round one. The round two Delphi questionnaire, shown below, asked the panel to rank their agreement with 4 statements.

3 of the 4 statements reached consensus, the remaining 1 statement was modified based upon unanimous feedback. The percentage in each score band for the Delphi statements in round two is shown in figure 3.4.2.

Percentage in each score band for the Delphi statements in round two



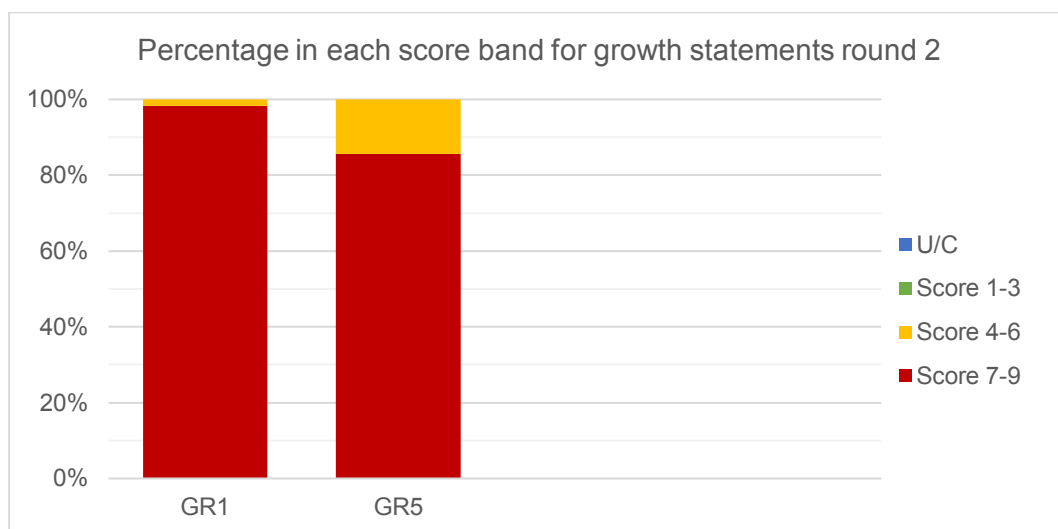
The following statements from round two reached consensus:

- GR1 If the history raises any concern, including parental concern about any aspect of growth, the child's height weight and head circumference (if under 2 years of age) should be measured and plotted on a growth chart.
- GR5 Brain tumours can present with rapid weight loss or faltering growth, however the differential diagnosis when presented with this symptom is wide. If a young person presents with rapid weight loss, the other signs and symptoms of a brain tumour should be specifically looked for as part of the assessment.
- B2 Brain tumours can manifest as with neuropsychiatric symptoms including new onset mood disturbance, withdrawal, disinhibition and pervasive lethargy. If a child or young person presents with these symptoms, the other signs and

symptoms of a brain tumour should be specifically looked for as part of the assessment.

RESULTS of ROUND TWO

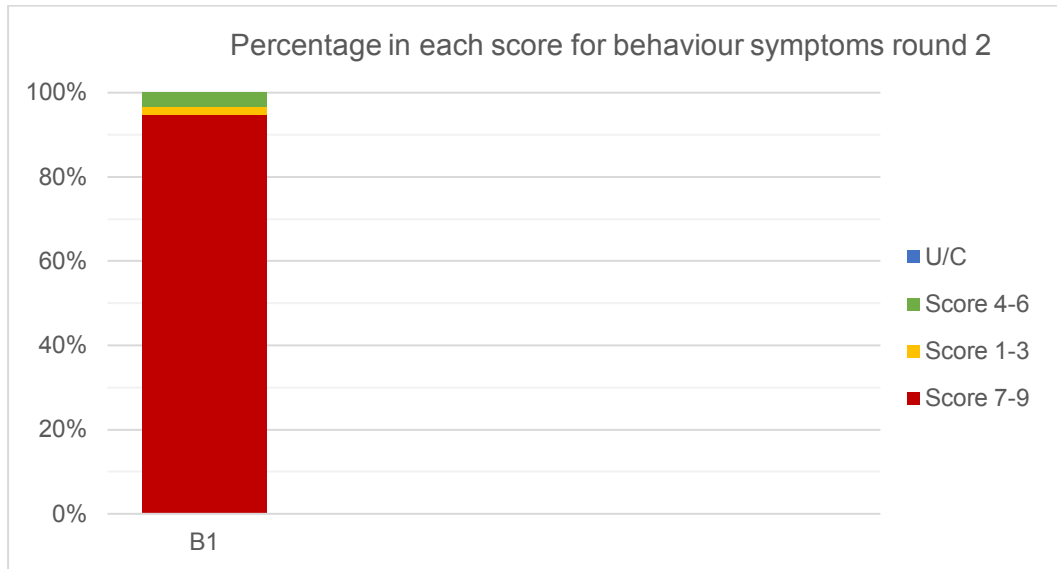
GROWTH STATEMENTS for Delphi Round 2:



The following two GROWTH SYSTEM statements achieved consensus in Round Two:

- GR1.** If the history raises any concern, including parental concern about any aspect of growth, the child's height weight and head circumference (if under 2 years of age) should be measured and plotted on a growth chart.
- GR5.** Brain tumours can present with rapid weight loss or faltering growth, however the differential diagnosis when presented with this symptom is wide. If a young person presents with rapid weight loss, the other signs and symptoms of a brain tumour should be specifically looked for as part of the assessment.

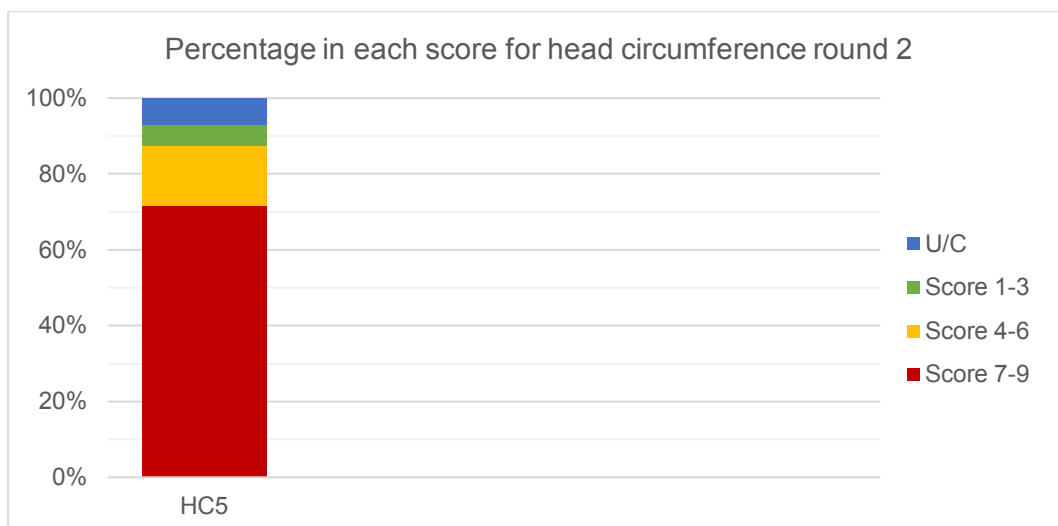
BEHAVIOUR SYMPTOMS STATEMENTS for Delphi Round 2:



The following BEHAVIOUR SYMPTOMS statement achieved consensus in Round Two:

- B2.** Brain tumours can manifest as with neuropsychiatric symptoms including new onset mood disturbance, withdrawal, disinhibition and pervasive lethargy. If a child or young person presents with these symptoms, the other signs and symptoms of a brain tumour should be specifically looked for as part of the assessment.

HEAD CIRCUMFERENCE STATEMENTS for Delphi Round 2:



The following HEAD CIRCUMFERENCE statement did NOT achieve consensus in Round Two, and have been modified.

HC5. In babies in whom a head circumference is increasing and a brain tumour is suspected an MRI is the imaging modality of choice within 4 WEEKS.

Outcome: This statement only received 71% consensus, however it was clear from the comments that the main reason for this was modified and sent out in Round 2 Delphi.

APPENDIX 9 Delphi questionnaire and comments

ROUND ONE RESULTS

BEST PRACTICE STATEMENTS for Delphi Round One:

CONSULTATION

C1. If a parent/carer expressed concerns about a brain tumour this should be reviewed carefully. If a brain tumour is unlikely the reasons why should be explained by reference to the symptom card/decision support tool and appropriate safety netting advice given.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

N/C ☐

Comments: 79.65%

Would be most unwise to practice any other way

strongly agree with first sentence but not second sentence

Don't use a symptom card but follow local clinical guidelines

Parents know their children best and should at all time be listened to and given thorough robust explanations as to possible diagnoses

do not currently use symptom card. Would assess careful and discuss red flags

don't currently use the decision card with parents

It depends on the level of anxiety & how reassuring you can be. In theory it makes very good logical sense but in practice I think we can all admit to arranging imaging based on parental anxiety.

The symptom card is useful in assisting the clinician in allaying fears parents have

The reasons why should be explained by reference to red flag symptoms. A symptom card is useful if available. Appropriate safety netting should always be given.

Sometimes parents need more Reassuring than a card

think would read better... P/c expresses (not expressed), explained with (not by)

Old adage of neurosurgery " Mum is always right"

I would explain - but not by reference to card/tool.

If underlying concerns were causing much anxiety or school loss, or if there were a family history of SOL or severe illness, I might be inclined to image sooner for peace of mind of family

C2. If a child warrants a review, the timing of this review should comply with national diagnosis of all cancers (currently, diagnosis or all clear should be given to the patient within 4 weeks).

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

N/C ☐

Comments: 83.04%

Hmm. We have to make some tough decisions about who loses out though! Resources are scarce

not sure what this means Is this a child with suspected brain tumour? if so i strongly agree

Although may not be possible and many of these patients may come through as "headaches"

Should be seen asap

Warrants a review implies does need imaging based on clinical assessment

That depends on the referral letter, which should probably be written with clear detail of worrying features, rather than simply 'headache' if needing to be considered as urgent

My experience is that nothing would usually change over that time frame so I would review later than that but emphasising red flags to contact directly & seek earlier review

There needs to be caution with this type of statement. It depends on who deems the review is needed and by what criteria. Many of the 2 week wait referrals that we get are for children who have had headaches for several years. Might be better to say if a brain tumour is strongly suspected or similar

It depends on the presenting symptoms and signs. Headache alone might not warrant such an early review, whereas red flag symptoms should.

Somehow the time for Giving Diagnosis should be ASAP

I feel all children with suspected cancer should be seen within a week but ideally within 2 days. I Think 4 weeks is far too long for a child to wait.

sometimes teh timeframe is too soon but reasonable to go with expert opinion

"or all clear" - not sure exactly what is meant in terms of 'the review'

This statement is unclear - if the diagnosis has been made, then formal biopsies etc and histology are warranted urgently. If the child with headache is being reviewed with a symptom diary, or having stated treatment, then this may be dependent on the availability of clinic slots eg. 6 weeks or 3 months. What is meant by review here?

Agree that it should comply, but it might need to be a lot quicker. This is not a target it is the lowest common denominator

C3. Some predisposing factors (personal or family history of brain tumour, leukaemia, sarcoma and early onset breast cancer; prior therapeutic CNS radiation; NF1/2; tuberous sclerosis) are associated with an increased risk of childhood brain tumours. Patients/parents should be specifically asked about these factors in consultation as their presence may lower the threshold for referral and investigation.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree

N/C ☐

Comments: 89.83%

The more predisposing factors present , the higher the possibility of finding pathology

Although I'm not sure many clinicians will know to ask about specific cancers e.g sarcoma, rather than 'family history of cancer'

This should be part of a normal medical history of all patients

Only refer those supsected of having brain tumour based on symptoms

this has to be balanced against raising anxiety levels so to be handled carefully

Family history of brain tumours should be asked. If they had already had prior therapeutic CNS radiation or NF1/2 or TS then this would already be known.

Ok. These are rare conditions. They are unlikely to be a priority in assessing the patient.

I always ask about past medical history but I do not usually name these specific diagnoses as I feel they may heighten anxiety unnecessarily

Agree, but can we specify where this consultation is taking place, or do we assume GP for all?

C4. Low parental educational level, social deprivation and lack of familiarity with the UK healthcare system may be associated with diagnostic delay. Care must be taken for appropriate safety netting and multi-disciplinary approach in these families.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
N/C ☐

Comments: 86.44%

Care must be taken for all families

I recognise that these 'may' delay diagnosis but would encourage the primary care team to support the family rather than overemphasise the symptoms to look out for

NHS has a tendency to be slow but needs interpretation

What do you mean by multi-disciplinary approach, in the context of primary care assessment?

REFERRAL

R1. A child referred from primary care in which the differential diagnosis includes a possible space-occupying lesion should be seen in a rapid-access clinic or similar service (ie within 2 weeks)

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
N/C ☐

Comments: 79.31%

The problem is Vomiting is a non-specific symptom so would get too many referrals - need specific indications for urgent review

same day review would help the family more

often these children by-pass the outpatient route and present at ED and be worked up appropriately/scanned etc.

A valid reason should be stated as to why a SOL is being contemplated

Agree although timing very much depends on clinical suspicion -may need to be same day referral although equally if suspicion low a longer interval may be appropriate.

this still seems a long time to me. For some this may be appropriate but some should really be same day. maybe needs qualification.

If the referral defines suggestive features appropriately

Not ED

This is difficult as many children with headache have this diagnosis in the differential and we cannot see all children with headache in 2 weeks

This is already in place with 2 week cancer wait. I think we have to be careful as any headache could include SOL as differential & we could not cope with this but attention to red flag alerts in primary care would help ensure most appropriate patients at risk are seen as a priority.

Slots should be reserved for cases like these as at present the local rapid access clinic is oversubscribed

There are variable quality referrals from primary care that make triage difficult

A child seen in primary care where there are concerns about a SOL should be discussed with the on call team so that appropriate review can be arranged. (In my experience 2 week wait can delay things, we would often see these children sooner if the history is really suggestive of a SOL. Often they will end up waiting 2 weeks rather than being seen and sorted sooner).

Depends on symptoms / signs. Headache alone: no; red flag symptoms (early morning headache): yes

That's where it should be quick rather than waiting

Yes but ideally within a week

I think if clear cut should be seen on the day, my impression is that there has not been more than 1 tumour of any sort found in a 2WW slot, better if that is the risk to see on that or following day

Reservation is that primary-care frequently raise this option and frequently the story does support.

Ideally as soon as is possible (within days)

This would depend on associated other symptoms mentioned in the referral

In fact, should be seen straight away

Or sooner via emergency department if there are concerns about raised intracranial pressure

Or on the same day on the assessment unit

IMAGING

IM1. A child in whom CNS imaging is required to exclude a brain tumour (potential diagnosis but low index of suspicion) should be imaged and reported within 4 weeks to meet Department of health recommendations.

Strongly Disagree

1

☐

2

☐

3

☐

4

☐

5

☐

6

☐

7

☐

8

☐

9

☐

Strongly Agree

N/C ☐

Comments: 82.76%

The anxiety is huge turnaround has to be a few days at most this is too slow

Should be sooner - 4 weeks feels like a long time for the family to wait

Similar to above in that timing will be influenced by degree of suspicion. It is essential that the report is timely and fed back to the referring clinician ASAP.

If there is a low index of suspicion 4 weeks deadline may not be needed

If a child needs GA this is very difficult to attain and despite good practice, know is practically hard to do

4 weeks would be nice, but unrealistic and unnecessary if the index of suspicion is low.

Earlier the better

Due to understandable high parental anxiety I feel imagine should be done quicker than adult cases, perhaps within 2 weeks.

If a child needs a scan to exclude a tumour this should be done within 1-2 weeks. I feel 4 weeks is too long to wait.

sooner if possible

Loaded question!! If it is DoH recommendation

Needs to be much sooner than that

IM2. The need to sedate or anaesthetise a child for imaging should not delay diagnosis and should be compliant with Department of Health guidance.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree

N/C ☐

Comments: 93.22%

with due diligence to the needs of the child

our hospital has recently introduced an onsite MR scanner (previously on the adult hospital site , access is much easier.

The need for sedation of GA should have nothing to do with the urgency of a scan

But in practical terms , this does limit using the best modality sometimes ie CT easier than MRI for many centres

SHOULD not delay but in the real world it MAY delay

difficult because of local availability of GA for scans. Would sometimes need to bring in as inpatient

I agree with statement but would need massive investment to deliver

I agree with the theory

Red flag symptoms: no.

Scan should still be done within 1-2 weeks

Loaded question!! If it is DoH recommendation

HEADACHE STATEMENTS for Delphi Round One:

H1. Headache is a common symptom and is very rarely, in isolation, due to a brain tumour. (refer to NICE headache guideline >12s)

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree

N/C ☐

Comments: 84.41%

agree but child must have a full neurological examination, full history including social and school history. In isolation with normal examination, not concerning but must be followed up.

I agree with this although isolated headache is commonly the initial symptom of a brain tumour. As such a detailed history is essential.

I would agree for an over 12 but for a younger child i would disagree.

Although the type, timing and chronicity of the headache may give additional information

I think this is clear and appropriate

Headache is a common symptom and rarely occurs in isolation if due to a brain a tumour. or Headache is a common symptom in CYP and is rarely due to a brain tumour if it occurs in isolation of other signs and symptoms. why reference >12s, i see lots of headache <12y. if this only applies to YP then say so in statement

This depends on age for me - headache is very uncommon in younger children !

Age dependent. I would be very suspicious in a child of 5 or under who made this specific complaint. Strongly agree for older children

H2. Any child presenting with a headache should be assessed carefully for the other symptoms of a brain tumour, as listed in the guideline.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree

N/C ☐

Comments: 96.55%

thorough history and examination is essential

Any child presenting with headache should be assessed carefully to look for an underlying cause of the headache.

Numerous children have headaches and important to define severity/frequency/red flags

as above

H3. A child with headache without a clear cause requires careful review, the timing of which needs to be mindful of the differential diagnoses and national guidance.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree

N/C ☐

Comments: 81.03%

depends a little on the nature of the headache or associated symptomatology

If no abnormal findings / red flags most are suitable for GP follow up as booked by the family

we would refer to rapid response outpatient clinic and keep a diary of associated symptoms, etc. seen within 2 weeks.

As stated above, headache alone is not associated with brain tumours

Most childhood headaches do not have clear cause and if anxiety-related or functional, excessive investigation or over-reviewing can worsen things

Sometimes school age try to be smart

but not practical if you don't think it's a SOI to then have to see within 4w if you think it still might be albeit very unlikely. often no clear cause but sound tension like and no other symptoms

This will depend on the character and duration of headache, presence of other symptoms, and age

Loaded question!! careful review whatever the diagnosis!

What do you mean "without a clear cause?". Most headaches in children are migraines, and there is no diagnostic test to confirm or refute this diagnosis. Migraines can be very similar in symptoms to the early presentation of a brain tumour. The key here is communication with the parents/carers about the natural history of migraines vs SOLs, and to give clear safety netting advice re progressive sx, changes in personality, morning symptoms etc. Reviewing every child with a headache a week later, even if the parent feels they have recovered, is not practical or appropriate.

NAUSEA & VOMITING STATEMENTS for Delphi round One:

NV1. Persistent nausea and/or vomiting with 1 or more other symptoms/signs associated with a brain tumour (ie headache, visual symptoms, motor symptoms, growth and development abnormalities, behavioural change) require CNS imaging.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 91.38%

admission would usually be arranged and urgent CT brain. mr not usually available out of hours.

persistent needs defining here

need more clarity on time frame (what persistent means) otherwise lots of acutely unwell children could get imaged inappropriately

2 or more, rather than 1 or more? Growth problems and vomiting have many causes...

not sure what duration you are referring to

Need to emphasise persistent or define more clearly otherwise all children with migraines would be scanned by these criteria

clarification of what constitutes persistent nausea and/or vomiting might be helpful to make this statement more specific

What is persistent? Nausea/vomiting plus headache is not a symptom combination to trivialise at any age, but can often be viral in primary care. Vomiting plus any of the other symptoms is undoubtedly a reason for imaging

NV2. Young children under the age of 2 who may not be able to communicate other symptoms of raised intracranial pressure should have their head circumference monitored.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 78.94%

1st Golden Rule

Practically this is very difficult to do and error is huge here

in addition to a clinical review looking for red flag signs

Some comment as to frequency of monitoring would be helpful. Needs to be closely monitored as increasing head circumference is a late sign.

vomiting is also very common symptom and most young children with vomiting don't have a brain tumour. I think a careful clinical assessments mandatory. I would not always check HC in a 1-2 year old but would expect to plot for all children less than 12 months

persistent needs defining here

Vomiting under 2 years is very common and has many causes

Most likely cause of persistent vomiting in this age group is gastro-oesophageal reflux and need to make sure not overly medicalising essentially normal children

initial head circumference taken and in presence of other symptoms might be helpful ongoing

If symptoms are very suggestive of gastroesophageal reflux, then no. If unexplained then maybe.

Probably most useful to monitor head circumference up to age 1 year - less useful after that

VISUAL SYSTEM STATEMENTS for Delphi Round One:

V1. Parental / carer concern alone (including nursery staff) regarding a baby or young child's vision should be taken seriously and a referral for visual assessment should be made.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 96.55%

very important, we have a rapid access clinic that optometrist, opticians can access for urgent ophthalmological assessment.

Seen several babies present with late diagnoses of septo-optic dysplasia where parents had appropriate concerns about vision and were ignored.

Yes , recognising the difficulty in assessing vision in the youngest children, expert assistance should be sought

MOTOR SYSTEM STATEMENTS for Delphi Round One:

M1. A history of a change or deterioration in motor skills may indicate a brain tumour eg change in hand or foot preference, developmental regression

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 91.07%

it may - but there are many other possible explanations!!

Yes , regression especially

M2. History should enquire into subtle changes in motor skills e.g. loss of learned skills (computer games, sport, handwriting)

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 91.23%

May not be due to a brain tumour but require investigation regardless, as development should not regress.

Assessed

I don't always ask about this in detail, but should

M3. Assessment of a child's fine motor and visual-motor skills should include questioning or observation of:

- **handling of small objects e.g. cup, spoon, small toy**
- **handwriting in older children.**

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 96.55%

also do finger nose pointing test

Yes doing simple things

An assessment should be made of a CYP fine motor and visual-motor skills for example manipulation of beads, utilising utnesil, handwriting etc

I don't always examine for this in a short appointment but do ask about developmental skills

M4. CNS imaging is required for any child with focal neurological signs, for example:

- **regression in motor skills**
- **abnormal gait or co-ordination unless attributable to a non-neurological cause**
- **focal motor weakness**
- **swallowing difficulties (unless local cause)**
- **abnormal head position**

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 91.07%

not all focal motor weakness, Bells palsy, peripheral nerve damage, abnormal head position needs clarifying

final abnormal head position needs clarification

Please distinguish from torticollis which does not need head scans unless CT with 3D modelling needed for craniosynostosis

Include new-onset squint in the list (which I know could be included in 'focal motor weakness' but I have seen ignored twice by other practitioners in past 10 years and both times was a sign of serious intra-cranial pathology.

not so sure about abnormal head position, in the absence of other signs. the rest strongly agree

since almost all new diagnoses I have seen in the last few years have been in young children with torticollis, I am in favour of this being high up the list

do you need the examples? perhapsfocal neurological signs including swallowing difficulties (unless known local cause) and abnormal head position. i don't think regression in motor skills is a sign and should be under this question

Yes , but emphasise NEW FOCAL signs , and probably excluding isolated squint

GROWTH STATEMENTS for DELPHI Round One:

GR1. Height and weight should be routinely measured and plotted on the appropriate growth chart for every child at every contact with a healthcare professional.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 66.67%

1st Golden Rule

yes always for new contacts but when there is frequent contact and health professional very familiar with the child measurement may be omitted if not relevant to consultation

How achievable is accurate recording of height in a primary care setting? Lack of time in consultations and appropriate equipment may limit ability to achieve this. Careful questioning about growth important. Plotting height and weight should be routine in secondary / tertiary care settings.

standard practice

I agree with this although appreciate may be more difficult in Primary Care. OFC must also be plotted in under 2's.

every contact is little bit unachievable. does this mean GP, HV, every ward round etc. I know what means but needs to be clearer particularly if audits are going to be done of back of this

not appropriate to do height and weight and plotting for every ED contact, GP or outpatient may be appropriate

Difficult to implement this practically in primary care for every child, every time.

Regardless of what the child is being seen with!

this is not feasible for all contacts for example in primary care or with ED

Parents are always on guard if not children themselves are also alert because of peers

This would be ideal but sadly GP do not have adequate time to do this and address concerns brought to consultation

Impossible in GP setting

Appropriate for oncologist , not necessarily for neurosurgeon / ophthalmology etc if already done recently

No. Completely unworkable in primary care. As a surgery we see 50 children in an average day. We would need a full time HCA to do this work. If you provided us with the £20k/year recurrent funding needed for this (£100M national cost for 5000 practices), how much extra pathology would you pick up? I'm sure there would be more cost effective ways to spend that money.

Depends. Not for contact with GP for URTI, but weight at every and height 3 monthly for secondary and above presentations

GR2. A child with a height or weight outside the normal range (<0.4th or >99.8th centiles, crossing centiles due to increased or decreased velocity outside that expected for age/pubertal stage or parental target range) should be referred to secondary care for assessment of their growth (see centile charts).

Strongly Disagree ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 Strongly Agree
N/C ☐

Comments: 84.48%

Fall yes. obesity no.

depends if there is a clear reason and GP competent to assess, manage

really depends on clinical context

Single measurement outside normal range not helpful. Crossing centiles more important.

Unless clear dietary cause found at primary assessment

Referral of children with isolated obesity is unnecessary. Presence of complications mandates referral.

After confirmation of findings

Height more relevant than weight. Excess weight is pretty much always due to excessive calorie intake and if all obese children were referred to secondary care, that would involve 20% of all >11s!

I agree with the plan but there is a need to put this in context of family stature and the statement suggests this is only relevant if crossing centiles

but this is inherent in the use of growth charts

Our local wait for a routine Paediatric appointment is about 10 weeks.

GR3. Early referral to secondary care is required for children presenting with precocious puberty, delayed or arrested puberty, growth failure (see GR2 for definition), galactorrhoea, primary/secondary amenorrhoea or polyuria/polydipsia.

Strongly Disagree ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 Strongly Agree
N/C ☐

Comments: 87.93%

is growth failure the right term? faltering growth?

Would clarify to gonadotrophin dependent precocious puberty

Polyuria needs to be defined as lots of children drink more and hence pass more urine but agree with rest

Children with polyuria/polydipsia should have a blood glucose level checked there and then in primary care, with same day referral if raised. In toddlers, this is often due to habitual drinking, so asking for advice rather than immediate referral may be more appropriate first line.

This is a meaningless statement. What does "early referral" mean?

GR4. Tumours affecting the midline supratentorial part of the brain can also affect vision. In children presenting with the above symptoms in statement GR3 require a full visual assessment.

Strongly Disagree ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 Strongly Agree

N/C ☐

Comments: 82.46%

probably good practice, I don't always achieve this. It would depend on the age and sex of the child and presentation.

Not necessarily - too broad a list ie. polydipsia/ polydipsia more likely to be diabetes mellitus than diabetes insipidus - depends on full picture. Likely to need imaging anyway, then visual field testing depending on results.

does this mean the above symptoms mentioned in 21. GR3?

second sentence is confusing... Children who demonstrate concerning symptoms and signs of growth (as described in GR3) may require a visual assessment. I'm not sure they are all getting a VA... should they? eg polydip/polyuria - may be DM and they don't

By who?

GR5. If a young person presents with rapid weight loss/underweight, a careful assessment should be undertaken looking for the other signs and symptoms of a brain tumour. If none of these are present they should be referred for eating disorder assessment and care. Should there be any concerns about atypical clinical features the team should consult with a paediatrician experienced in eating disorders care to determine if further investigation is required. This should not delay referral to the CAMHS team.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

N/C ☐

Comments: 71.93%

Preferably concurrent paediatrics and CAMHS referrals and should have physical health risks due to weight loss monitored.

There really depends on multiple causes and factors

seem to have missed out consideration of non brain tumour organic pathology !(eg malabsorption's) surely this needs to be done before considering eating disorder!

Need to have broader differential than brain tumour and eating disorder for rapid weight loss, including other forms of malignancy and systemic disease.

extremely difficult access to eating disorder service (there isn't one), also CMAHS service very difficult to access, eating disorder diagnosis of exclusion. often imaging of the brain will have been carried out.

Agree although differential diagnosis is clearly very broad.

there are other differentials for weight loss other than brain tumours and eating disorders. these should surely be in the mix somewhere

There is a large differential diagnosis not included here: inflammatory bowel disease/ thyrotoxicosis etc. So only once physical causes excluded and dependent on suggestive features of eating disorder

other causes of weight loss need to be considered well before referral for eating disorder assessment and care

Good in theory but how many paediatricians declare an interest in eating disorders & how accessed ?

Depends on rate of weight loss

Don't forget other causes such as diabetes, inflammatory bowel disease or hyperthyroidism; important those are excluded before referring to CAMHS!

There are other medical causes to consider and exclude too rather than just brain tumour or eating disorder - such as inflammatory bowel disease

Long delay for camhs assessment would more likely refer to paed's to rule out non-psych disorder first

equally this could be coeliac disease or a GI problem. I'm not sure what the point is... rapid weight loss or underweight could be a number of diagnoses, the point about ED is reasonable but not in isolation

From brain tumour to anorexia - what about all the stuff in the middle - coeliac etc! Poor question

What if they are diabetic? Or have a swallowing problem? Do you still want me to refer to the eating disorders team, or am I allowed to be a doctor and use my judgement? I thought this was a guideline about brain tumours, not eating disorders.....

Yes, but there may be many other reasons other than eating disorders

BEHAVIOUR STATEMENTS for DELPHI Round One:

B1. Brain tumours can manifest with neuro-psychiatric symptoms.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

N/C ☐

Comments: 92.98%

'can' is loaded

Often not in isolation but can (craniopharyngioma / germ cell etc)

Not common.

However, I think this presentation is rare without other symptoms

CAMHS colleagues need guidance on who to refer for imaging

Age dependant

yes they CAN but most who present with these findings won't have a brain tumour in my experience

Yes , but much more commonly in adults / older adults in my experience

Yes, but rare.

B2. Pervasive lethargy is an under-recognised symptom in brain tumours and warrants careful assessment of the other symptoms in order to make a diagnosis.

Strongly Disagree 1 2 3 4 5 6 7 8 9 Strongly Agree
☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

N/C ☐

Comments: 57.14%

Also very common in all ages of children

Sorry not sure

Agree although again there is a very wide differential diagnosis.

i don't understand this. which other symptoms? diagnosis of what?

Pervasive lethargy warrants careful assessment.

Was not aware of this & opens up a can of worms with CFS / ME patients

the RCPCH guidance on CFS/ME does not suggest routine head scans

More likely to be non-organic in cause, though

although I am sure this can occur, again there are many other possible causes

Sometimes careful assessment does reveal signs

As a GP I am Previously unaware of this as a presenting feature

Most teenagers have pervasive lethargy?

Again - lots of other conditions produce lethargy

B3. Children presenting with new onset mood disturbance, withdrawal and disinhibition require careful assessment looking for other signs and symptoms of a brain tumour.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 82.15%

Also need to consider other physical health problems - thyroid, epilepsy etc
particularly in adolescents

As part of a thorough assessment of other possible causes.

need careful assessment for all causes - drugs, alcohol, psychiatric issues, safeguarding issues etc.

Relatively uncommon presentation in my experience

Again - lots of other conditions produce above.

HEAD CIRCUMFERENCE STATEMENTS for DELPHI Round One:

HC1. A rapidly increasing head circumference or macrocephaly can be a sign of an underlying brain tumour and requires referral to secondary care.

	1	2	3	4	5	6	7	8	9	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 93.1%

Or is a sign of hydrocephalus...or storage disorders etc

Thought should be more on hydrocephalus

USS may be sufficient to image if the fontanelle is open then proceed to mr/ct as indicated by the radiologist.

Agree for rapidly increasing head circumference (assuming measured correctly) but macrocephaly requires a bit more detail e.g. parental head sizes before secondary care required

also sign of other causes that require referral not just brain tumour

If just macrocephaly then this should be considered with ht and wt centiles, previous and parents HC should be checked first

initial head USS on day could help

May be sign of other pathology too but not really able to be assessed appropriately in primary care

If not brain tumour, at least hydrocephalus and needs urgent assessment.

again it can so the statement is correct, but is not the most common cause

Definitely seen it

perhaps liaison and not def referral ... in the babies we may monitor in primary care initially if no other symptoms

Yes to rapidly increasing head circ. This will more commonly be due to other cause of hydrocephalus but still needs rapid evaluation. Macrocephaly needs evaluated in context of family head size / other growth parameters and pace of development

HC2. A rapid increase of head circumference is defined as one that crosses 2 centiles on the head circumference growth chart.

Strongly Disagree ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ Strongly Agree

N/C ☐

Comments: 75.87%

Except when birth value used

Needs to have some mention of time period to qualify the use of rapid in the statement

Not sure of official; definition

Rapidity refers to rate of increase, not degree of increase. However a rise of 2 centiles would be a highly significant increase.

rapid also needs defining? this definition includes the degree of increased head size but not the rate. Maybe you mean significant increase

over a short period of time

over what time period? 6 months? or 6 weeks? or even one week? I prefer the middle one

Yes, but it depends on how fast it crosses the centile lines.

With other symptoms

need to define the time frame

needs a timeframe

Need to specify rate of crossing eg 2 centiles over a few weeks time

There is no mention of a time frame here

Not sure what the actual definition is but this is probably true

No. That is a clinically significant change, but rapidity is based on the time interval between the changes, not the magnitude of the change

HC3. If a healthcare professional has concerns that a baby has an increasing head circumference or macrocephaly in relation to its height and weight, but has not crossed threshold for referral then provided the baby is otherwise asymptomatic 2 weekly monitoring of the head circumference is appropriate.

Strongly Disagree ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ Strongly Agree

N/C ☐

Comments: 63.79%

depends on level of anxiety of parents sometimes better to get scan early and completely reassure

has to be in clinical context of no other signs or symptoms to do this

not sure, referral to paediatrician would seem reasonable for neurological assessment.

Agree, although does depend on other factors -including reliability of OFC measurement.

Measure parents heads too - ? familial

Likely to discuss this type of case with a Paediatrician

need to check for family history of macrocephaly

Monthly in a well baby

Explanation to the parents

Parental OFC is also important as may be familial macrocephaly in well child.

what is the threshold - that is confusing. i agree with the sentiment.. why not remove "but has not crossed the threshold for referral" and say provided the baby is otherwise well, entirely asymptomatic then 2w.... This might need a "and if this happend liaise".

But also needs to be seen

Don't mess about. Refer them!

HC4. In all babies with an increasing head circumference, careful assessment of other symptoms of signs associated with a brain tumour should be undertaken.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 87.72%

yes as part of holistic assessment , but brain tumour not only pathology of concern!

Needs some reference to increasing head circumference crossing centiles rather than increasing along centile.

again attention to detail in infants is of paramount importance

careful assessment should be undertaken for all causes

Hydrocephalus not due to a brain tumour more likely but equally, needs urgent assessment and treatment

Should be urgently referred if other signs symptoms present.

Bad wording ! - all head circumferences increase- should be rephrased as rapidly increasing or concerning...

But there are other conditions which would need to be considered in general clinic - hydrocephalus is much more likely.

HC5. For a baby whose head circumference has been correctly plotted and increased by 2 centiles or more, an MRI is the imaging modality of choice within the appropriate timescale.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 71.93%

Although this is also anaesthetic dependent also with respect to timeframes

uss fist then see what is seen then MR if appropriate as ct in under ones has large radiation dose.

Cranial Ultrasound would probably be first investigation and then MRI if required

Agree although cranial ultrasound may be reasonable initially as long as a normal result is not interpreted as excluding a brain tumour.

I would usually arrange USS head first to assess for hydrocephalus but would then progress on to MRI within the timescales

cranial ultrasound is appropriate in some particularly where early hydrocephalus is main differential?

Agree that this is best, but may not be quickest

USS may be available sooner and may be requested in addition to MRI

Although MRI may eventually be needed I would have quicker access to a cranial ultrasound & would do this as the initial screen if anterior fontanelle open & progress to an MRI if obvious cause not apparent.

MRI is the scan of choice, but many babies will cross 2 centiles from their birth HC and then level out.

CT might be more appropriate and easier to obtain in a timely fashion to exclude obviously underlying tumour

depends on age of 'baby'; neonatal cranial ultrasound may help

Would Ultrasound first unless other concerns.

Uncertain of which imaging techniques are best

again agree with sentiment but it suggests all will need to have imaging.. why not MRI is the imaging modality of choice if there are concerns about the rate of head circumference growth in a baby. Just a little worried the HC questions may be confusing if all used as they almost contradict each other

Dependent on time frame and family history of large head size

If under 1 yr, I would do cranial ultrasound as first line of investigation

ROUND TWO RESULTS

GROWTH STATEMENTS for DELPHI ROUND 2

GR1. If the history raises any concern, including parental concern about any aspect of growth, the child's height weight and head circumference (if under 2 years of age) should be measured and plotted on a growth chart.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 98.24%

standard growth chart or specific for any chromosomal syndromes

Does this include in primary care/ community?

Plotting growth on centile charts is fundamental in paediatrics and should be performed whenever possible.

This should be done as a matter of course

This should be routine for any child at any medical contact

This should be done for all children.

1st golden rule of paediatrics. Truth be told - I think all children should have height and weight plotted. Head circumference - may be more difficult for older children and less useful.

This is a very vague statement which is why it's difficult to answer

I have seen that together all these parameters are helpful

this should be standard practice

Surely should be part of any assesment wether tumour related or not

Check head circumference at any age

GR5. Brain tumours can present with rapid weight loss or faltering growth, however the differential diagnosis when presented with this symptom is wide. If a young person presents with rapid weight loss, the other signs and symptoms of a brain tumour should be specifically looked for as part of the assessment.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 85.81%

See BMJ paper from about 9-10 years ago of 'anorexia nervosa' in boys turning out to be due to brain tumours

Other conditions far more common cause of weight loss and it would be unusual to present solely with weight loss in brain tumour in older children

A brain tumour would be a rare cause of faltering growth given the very wide range of other causes. It would be reasonable to consider it if there was another pointer in the history or examination to suggest the possibility of neurological involvement. I wonder if the statement could say "If a child or young person presents with this symptom and has any other neurological signs or symptoms, other possible features of a brain tumour should be specifically looked for".

Rapid weight loss and brain tumours occur but not commonly

The differential is wide. Fluctuating growth is significant - but not necessarily specific for brain tumour. A cause needs to be sought.

I would phrase this as rapid weight loss in children or fluctuating growth in young people rather than the other way around

Again I have found no weight loss but brain tumour

Slightly unreal question as symptom requires a full history. Not 'strongly' as other features of history would also direct - i.e. dietary intake, output - but one would ask for 'any other concerns/features'.

neurological examination should be part of thorough history and examination

Unusual but important differential to consider

Should have comprehensive assessment to exclude all causes of weight loss.

BEHAVIOUR STATEMENTS for DELPHI ROUND 2:

B2. Brain tumours can manifest as with neuropsychiatric symptoms including new onset mood disturbance, withdrawal, disinhibition and pervasive lethargy. If a child or young person presents with these symptoms, the other signs and symptoms of a brain tumour should be specifically looked for as part of the assessment.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									

Comments: 94.74%

A little more specific. However, it is important to bear in mind that many teenagers will have low mood, withdrawal and brain tumour is a very rare cause when considering the numbers presenting with this condition.

Yes. There does need to be a formal neurological examination including tests for ataxia and fundoscopy and if these cannot be performed for whatever reason the patient should have an expedited scan or specialist review

Parents when come with this complaint need to be assessed thoroughly

Slightly unreal question as symptom requires a full history. Not 'strongly' as other features of history would also direct - i.e. home/school/lifestyle - but one would ask for 'any other concerns/features'.

can be difficult to assess, must listen to the parents who know the child best

Slightly cautious as could open up a raft of referrals from CAMHS & Psychology.

As well as other physical health conditions and psychiatric disorders that might explain presentation.

HEAD CIRCUMFERENCE STATEMENTS for DELPHI ROUND 2

HC5. In babies in whom a head circumference is increasing and a brain tumour is suspected an MRI is the imaging modality of choice within the appropriate timescale.

	1	2	3	4	5	6	7	8	9	
Strongly Disagree	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Strongly Agree
N/C	<input type="checkbox"/>									
Comments: 71.42%										
i think should be sooner										
within 4 weeks. may need to be sooner than this in many situations. Which guidance- ref please.										
if available										
Many hospitals still have problems obtaining MRI under GA within this toe, so other scanning modalities may be needed first										
Cranial ultrasound is a reasonable first line investigation but a normal study does not exclude pathology.										
Unable to comment on most appropriate imaging or timescale. Under these circumstances I would be referring or admitting depending on child's condition										
Cranial ultrasound would be the first investigation of choice										
Depends on the association of other symptoms or clinical signs. Eg if sun setting eyes or other symptoms signs suggestive imong raised IVP then a Ct scan can be arranged much more urgently and easily										
Not my field of expertise. 4 weeks sounds like a long time to wait though.										
Caveat to this is if they are systemically unwell in which case a CT would be obtained from the ED										
I would do a US head first. Probably can get organised within 24 hours and important to do quickly. Many DGHs will struggle and there will be lots of failed MRI scans! I guess it depends on the degree of suspicion for 'brain tumour'. A child with abnormal new focal neurology will get a MRI. A child with probably hydrocephalus will get US.										
4 weeks is far too long. These babies should be referred for specialist paediatric review within 24 hours										
Ultrasound useful first line to escape GA for MRI										
Don't understand this waiting period why?										
In babies in whom head circumference is rapidly increasing and a brain tumour is not suspected then a cranial US should be performed urgently. If a brain tumour is suspected or an US is not practical an urgent MRI scan should be performed. (I would personally always do within 2 wks as 4 weeks seems very long)										
4 weeks feels quite long. If I was worried about an increasing head circumference I would aim ot see the infant more quickly than this and arrange MRI within 7-10 days (probaly much less in reality)										
Have I read this right? Surely 4 weeks is not the recommended max wait for a rapidly increasing HC with a suspicion of tumour this should warrant and URGENT scan I agree that MRI is appropriate modality but not the timescale!										
But waiting four weeks with strong suspicion is too long										
There may be a place for CT as this is more accessible and tolerated without sedation. In majority MRI would be first line but CT should also have a place.										
Certainly less time than 4 weeks - would go and speak to neuro-radiology										
Should be performed acutely										
It depends on degree of suspicion. If a tumour is most likely then I would strongly agree but in babies usually other causes are more likely eg. intracranial haemorrhage, hydrocephalus etc. so I still think an early screening (say 2 weeks) ultrasound when fontanelle open would direct further choice CT / MRI without delaying reaching outcome.										

APPENDIX 10 References for published papers

Wilne, S. H. et al. The diagnosis of brain tumours in children: a guideline to assist healthcare professionals in the assessment of children who may have a brain tumour. Archives of Disease in Childhood, 2010;95:534-539

Wilne, S. et al. Presentation of childhood CNS tumours: a systematic review and meta-analysis. The Lancet Oncology, 2007. 8(8): p. 685-695.

HeadSmart: Be Brain Tumour Aware. A new clinical guideline from the Royal College of Paediatrics and Child Health with a national awareness campaign accelerates brain tumor diagnosis in UK children – “HeadSmart: Be Brain Tumour Aware.” Neuro- Oncology. 2015; 0-1-10; doi:10.1093/neuonc/nov187.