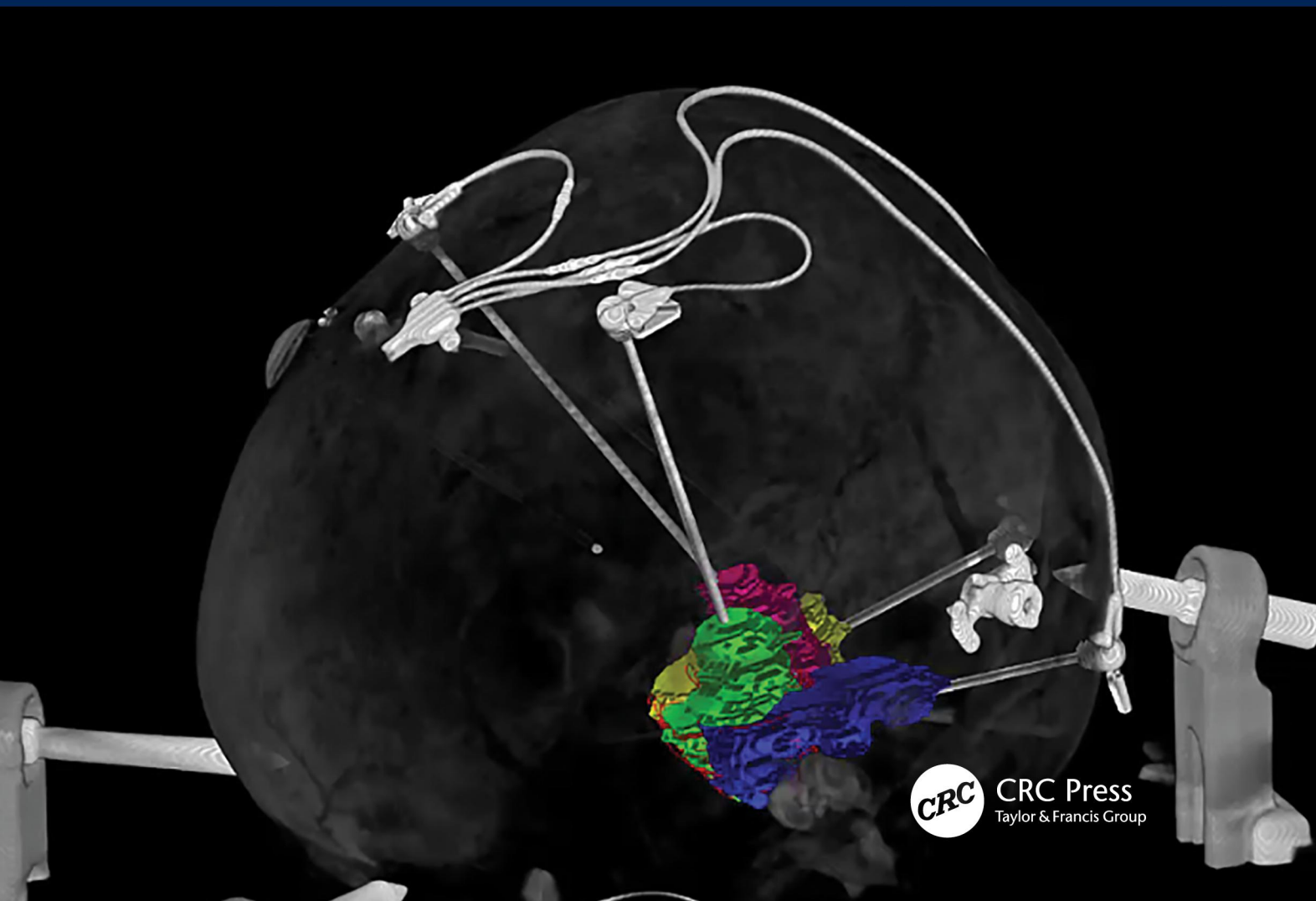
Brain and Spinal Tumors of Childhood

Second Edition

Edited by
David A. Walker
Giorgio Perilongo
Roger E. Taylor
Ian F. Pollack



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Introduction

1

DAVID A. WALKER, GIORGIO PERILONGO, ROGER E. TAYLOR, and IAN F. POLLACK

1.1 WHY A SECOND EDITION OF THIS BOOK?

The first edition was the first European book to be published that focused upon the clinical management of childhood brain tumors and the associated translational scientific evidence in a single volume. As editors, we were aware of breaking this new ground and made our introductory chapter focus upon the timeline of scientific and clinical discoveries that had led up to the level of knowledge of science and practice that existed at that time. For this second edition we considered extending the timeline to cover the developments that have occurred in the interim, particularly the understanding of biological parameters and their impact on outcomes and clinical management. We concluded, however, that the explosion of knowledge was too extensive to summarize and the true impact of each development was too early to fully evaluate in a historical sense. We have lived and practiced through the past years during a paradigm shift. It is exciting but we are not entirely sure where it will take us. The greater understanding of tumor biology has also resulted in questions regarding how this should impact on treatment decisions.

The second edition of this book has therefore undergone an extensive revision to take into account the new evidence from science and practice, supporting modern approaches to the clinical presentations of childhood brain tumors. The processes needed for their timely, molecular-based diagnosis as well as neurosurgical and radiotherapy techniques are described. The pediatric medical management aimed at eradicating the tumor and the design of trials to test and evaluate new approaches are discussed. Equally important is the need to measure and understand the impact of the tumor and its treatment upon the full functioning of the developing brain of the child. This has implications acutely in the time leading up to diagnosis and during subsequent treatment. It also contributes to judgments of the risks of acquiring dysfunction or disability, with the risk of death and the inevitable consequences on quality of life for those who survive. Finally, the advances we have seen have been strongly supported and guided by a wide range of advocates across the world, who have been touched by the experience of children with brain tumors and shared their experience in the chapter on advocacy.

1.2 WHAT CAN THE READER EXPECT IN THIS BOOK?

This is not a textbook covering every aspect of the science and practice of pediatric neuro-oncology as that would need to encompass the whole of developmental neuroscience, cancer biology, and the application of multidisciplinary clinical care for children in hospital, in the community, in their education, and ultimately, in their adult life. Rather, this book is a series of authoritative statements written by international experts working as multidisciplinary collaborative groups, who have first-hand experience with how treatments have been influenced by science and delivered to children and how the scientific processes will influence the approaches in the future. The aim of the editors has been to establish an appropriate balance of authors from North America and Europe.

1.3 THE SCOPE OF CHALLENGE: SURVIVAL VERSUS DISABILITY

In industrialized countries with comprehensive health systems, the majority (~65%) of children presenting with brain tumors can be offered a chance of prolonged survival. Sadly, however, about the same proportion (~60%) can be expected to have moderate or severe lifelong disability. The diverse scope of childhood brain tumors is illustrated by the image of the ten typical brain tumors of childhood (Figure 1.1).

The benign or low-grade brain tumors identified above threaten local brain injury due to tumor progression or surgery for their removal. Where such tumors are not amenable for surgical removal, the risk of progressive focal brain injury may be modified by non-surgical treatments directed at reducing tumor bulk or preventing tumor progression, thereby arresting progression of the brain damage with which they presented. These tumors often stop growing as the child ages, although there are exceptions. The malignant or high-grade brain tumors present the additional threat of leptomeningeal metastatic dissemination and therefore the need for effective therapy to be delivered to the whole of the brain and spine to offer cure.

In this collection of tumors there are good players (Figure 1.1), where survival can be expected, often after a single operation. At the other end of the scale, there are very poor players where survival is exceptional because treatment is currently impotent. For those in the middle the various approaches to treatment are described. Progress is being made. However, the predominance of the more optimistic survival figures highlights the importance of giving equal consideration to the risks of disability *and* survival. For those who survive, the disability is lifelong and life altering. However the ability of the healthcare system to support patients with disabilities will also be taken into account, as will the attitude of parents and carers. For children with poor prognosis, this burden of disability and its progressive nature is the focus of palliative strategies. These differ from other cancers in childhood, as the symptoms requiring palliation are due to raised intracranial pressure or progressive brain damage, rather than metastatic disease.

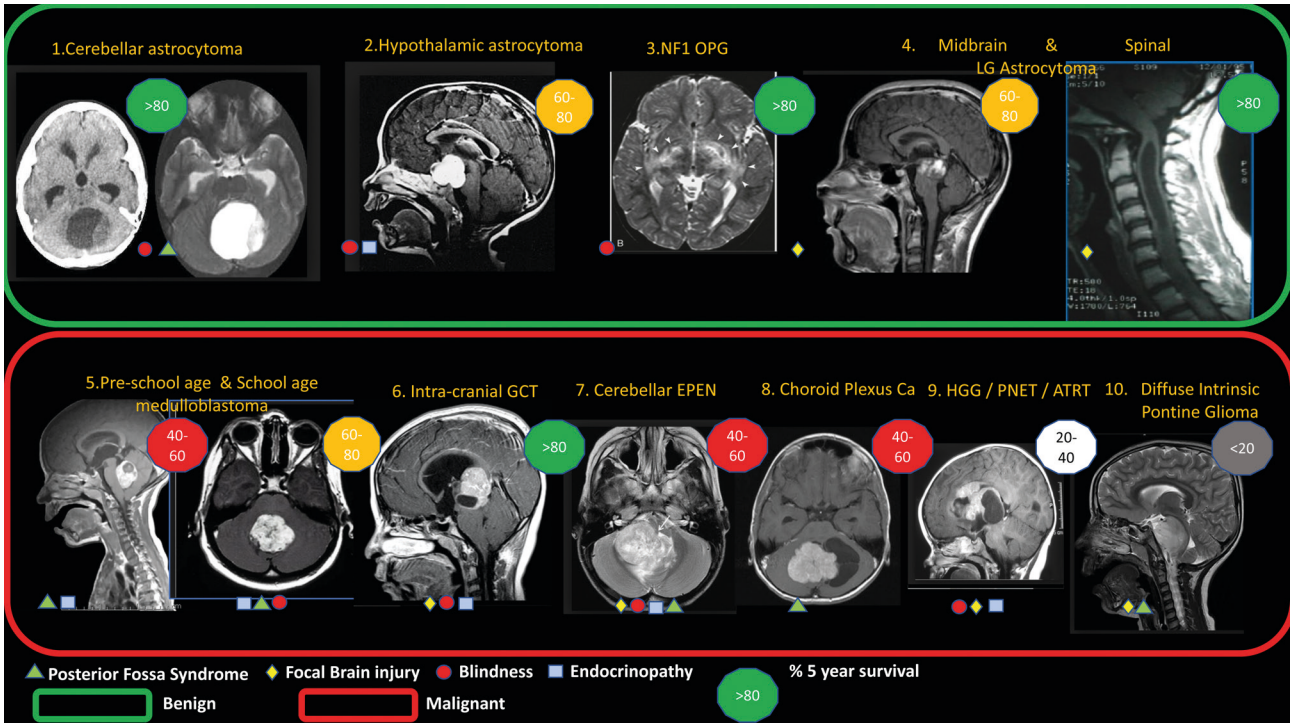

Figure 1.1 The anatomical features of ten common brain tumors in children, highlighting the predominance of low-grade glioma (green box) and range of malignant tumor types (red box). Benign tumors are slower growing with low risk of metastasis. Malignant tumors are faster growing and have a higher risk of metastasis. Symbols illustrate typical late consequences of the tumor and its treatment for survivors; cerebellar / cognitive refers to consequences of cerebellar mutism / posterior fossa syndrome and prolonged hydrocephalus upon late cognitive function. Focal injury identifies the risk of focal brain injury related to tumor or surgery. Blindness is as a consequence of tumor damage to optic tracts or prolonged raised intracranial pressure. Endocrinopathy is due to hydrocephalic / pituitary damage from tumor or surgery or radiation therapy. The figure illustrates typical population-based 5-year survival rates. ATRT, atypical teratoid rhabdoid tumor; Ca, carcinoma; EPEN, ependymoma; GCT, germ cell tumor; HGG, high-grade glioma; LG, low-grade; NF1 OPG, neurofibromatosis type 1 optic pathway glioma; PNET, primitive neuroectodermal tumor.

Management of these patients continues to pose very difficult ethical issues regarding the balance of survival vs. the quality of that survival.

1.4 BIO-INFORMATION EXPLOSION

If there is a single factor that has supported the transformation of scientific understanding in this field over the past decade, it has been linked to the collaborative development of large clinical datasets associated with biosample banks arising from extraordinary collaborations on a global scale. Translational clinical scientists have worked tirelessly to explain the clinical phenomena we observe in practice by studying detailed biological processes involving these tumors of the developing brain. They have openly shared the resources from their laboratories and their clinical trials datasets and adopted sophisticated international consensus techniques to make the best of the information that is available to them. This work has identified an increasing number of inherited predisposition states for brain tumor development and a lengthening list of genetic and epigenetic mutations that characterize sporadically occurring tumor types, which are the majority. The language describing these tumor phenomena is fluid, creating new diagnostic and clinical entities with the consequence of significant uncertainty for the clinician in knowing exactly what treatment to offer, based upon the complex scientific description of the tumor in the child's brain. The work is progressing in parallel with the study of neuro-embryology as the genetic and epigenetic mutations identified in the tumors are increasingly being mapped to specific anatomical regions and associated with specific age of tumor presentation or recurrence. Identifying the mutations, which are functional for tumor cell behavior, is the challenge. To date, there has been only one drug launched with specific molecular targeting, which has been licensed for clinical practice in brain tumors. Everolimus, an mTOR inhibitor, is licensed in the USA and Europe for the treatment of subependymal giant cell astrocytoma (SEGA) complicating the genetic condition, tuberous sclerosis complex. We await results of trials of other targeted agents. The most hopeful at the time of writing in 2020 are the mitogen activated protein (MAP) kinase-targeted drugs in low-grade glioma and plexiform neurofibroma associated with neurofibromatosis type 1.

1.5 DELIVERING THERAPIES TO THE BRAIN

Neurosurgery and radiotherapy are the mainstay of effective brain tumor therapy because they are applied directly to

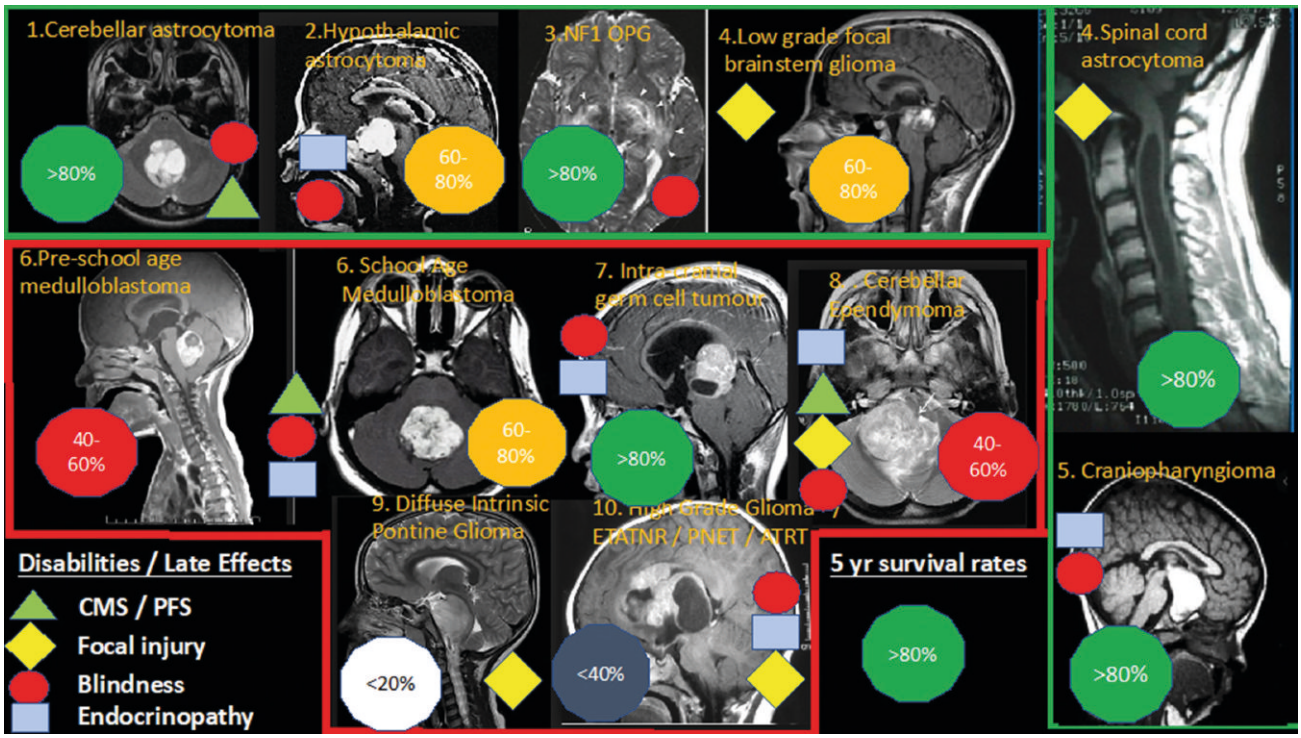

Figure 1.2 Anatomical drug-targeting research considerations. BBB, blood–brain barrier; CNS, central nervous system; ICSF, intracerebrospinal fluid; IV, intravenously.

the brain. Neuroimaging is extremely sophisticated and can specify the anatomical location of the tumor precisely. In the last decade in many countries the delivery of radiotherapy has been radically transformed by the application of proton therapy with its ability to minimize or avoid radiation dose to non-target tissues, and is described in this book. Furthermore continued advances in the delivery technology for proton therapy have not reached a plateau. Much of the evidence for benefit is still based on dosimetric comparisons and modeling predictions of toxicity reduction. There are increasing numbers of case series, but developing randomized trials comparing proton with photon therapy with respect to long-term toxicity reduction, many years or even decades later, is problematic. Data collection, including "real-world" data, will remain an important priority.

Drug therapy is confounded by the protective nature of the blood–brain barrier when drugs are administered systemically via the blood stream. The science behind techniques to modify drugs to assist with their penetration of the blood–brain barrier is in development. Techniques to disrupt the blood–brain barrier to facilitate drug passage are in trial. Techniques to bypass the blood–brain barrier and deliver to the cerebrospinal fluid are in widespread use in childhood leukemia but are only slowly being adopted in brain tumors. Delivery of drugs to tumor cavities and directly to the tumor tissues is now feasible with surgical techniques. Transmucosal drug delivery has been explored with cannabinoid drugs in adult brain tumor. In adult practice, electric field therapy has been studied in a single randomized clinical trial, with a favorable result, there is supporting biological literature, and technical modifications of the electric field systems are in process. Immune therapy is being adopted for childhood leukemia and tested in adult cancers, although early reports are not promising for the treatment of brain tumors. There is therefore no shortage of new ideas for therapy in this group of diseases. The mistake would be to continue to disregard the mechanisms for ensuring that any treatment is delivered to the correct part of the brain and in effective quantities in future trials. There remains the challenge of ensuring the introduction of new brain-directed therapies includes the requirement for monitoring for long-term sequelae in survivors (Figure 1.2).

1.6 GLOBALIZATION OF PEDIATRIC NEURO-ONCOLOGY

This book is a product of work carried out mainly in high-income, industrialized societies with established or emerging comprehensive health systems for children. As brain tumors are a byproduct of normal brain growth and development, they are seen to occur in all societies and indeed the experience is that the more you look in developing countries' health systems, the more cases you find. It is a sad reality that in low- and middle-income countries many children with cancer, including brain tumors, will not receive optimal care. With their discovery comes the need for the development of specialized programs of care. The World Health Organization has recently launched their Global Initiative for Childhood Cancer (www.who.int/cancer/childhood-cancer/en/). In their comprehensive

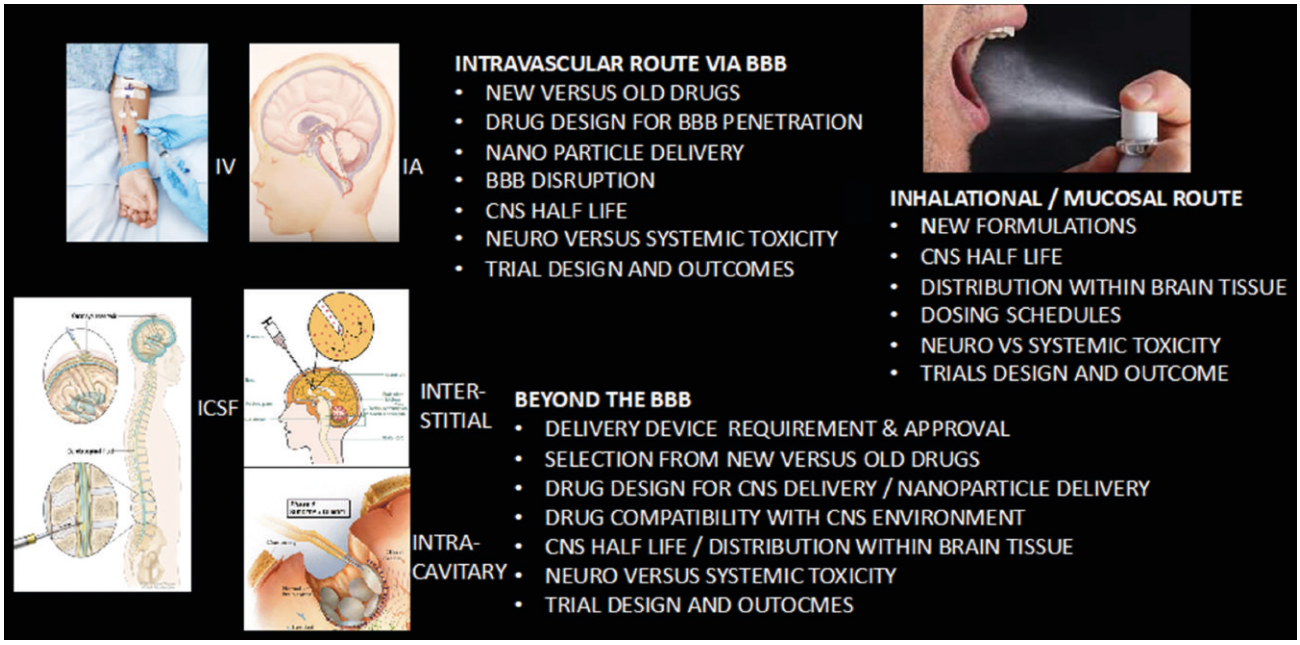

Figure 1.3 Global initiative for childhood cancer: index cancers. (Reproduced from World Health Organization, www.who.int/cancer/childhood-cancer/en/, under open access.)

plan they have set the target that "by 2030, achieve at least 60% survival rate for cancer globally, and reduce suffering for all."

From a neuro-oncology perspective low-grade gliomas have been selected as the index cancer for this initiative (Figure 1.3).

They have identified a CURE All strategy to deliver to selected countries:

- **C**enters of excellence and care networks that are fit for purpose
- **U**niversal health coverage for essential quality services
- **R**egimens and roadmaps for diagnosis and treatment
- **E**valuation and monitoring, with robust information systems and research
- **A**dvocacy
- **L**everaged financing
- **L**inked governance

1.7 THE FUTURE OF PEDIATRIC NEURO-ONCOLOGY

The first edition of this book reflected the establishment of pediatric neuro-oncology as a discipline. The launch of this second edition comes at a time of great change. We now have a much stronger understanding of the clinical practice and the neuroscience of these tumors and their mechanisms of growth within the developing brain. We have excellent collaborative translational networks and many ideas to explore in future trials and scientific initiatives. Our advocates should take note that their work has not gone unnoticed. The world has woken up to the disparity in access to modern therapies and outcomes across global communities for children with cancer, including brain tumors, and has made a commitment to reduce them. For those considering a career in medicine or science related to this group of childhood diseases, the future is bright and this book is designed to kindle your interest. The children and their families need your help.

Epidemiology of Childhood Brain Tumors

2

RICHARD J. MCNALLY and PAUL GRAHAM FISHER

2.1 INTRODUCTION

Central nervous system (CNS) tumors in children are a heterogeneous collection of neoplasms ranging from benign (low-grade, World Health Organization (WHO) grades I and II) to malignant (high-grade, WHO grades III and IV) histology and behavior and arising primarily in the brain or spine. These tumors are often referred to collectively as childhood brain tumors, which will be the practice in this chapter. Past studies have variably included children under age 15 years, or sometimes under age 19.

While the occurrence of brain tumors as a group is second in childhood cancer incidence only to the leukemias (principally acute lymphoblastic leukemia and acute myelogenous leukemia), the breadth and diversity of brain tumors far exceed that observed in any other organ system. Consequently, epidemiology has frequently lumped childhood brain tumors together when examining potential exposures, particularly environmental agents or parental characteristics, as potentially causal or predisposing to a tumor. This practice is understandable given the overall uncommonality of childhood cancer, then split into types of childhood tumors, and further divided into myriad subtypes of childhood brain tumors.

In 2016 the WHO restructured significantly the classification of brain tumors to incorporate both histology and molecular genetic features.[1] This revision thus requires us to reconceptualize to some extent prior epidemiologic investigations using diagnostic labels no longer used (e.g., primitive neuroectodermal tumor [PNET]) or agnostic to newly recognized entities, variants, and patterns (e.g., diffuse midline glioma). Such shifting of classification allows now for greater precision in identifying tumors that are distinctly similar in biology, tumorigenesis, and perhaps cause. At the same time, these changes present some problems to epidemiology. Some childhood brain tumor subtypes are so uncommon that even some of the world's larger countries often witness less than 100 or 50 of a particular tumor in any given year. Perhaps more troubling is that prior epidemiologic research, using different diagnostic groupings or pooling of all childhood brain tumors together, may be subject to misclassification bias and potentially false identification or false exclusion of some exposures possibly important to etiology. Such methodological problems are inescapable in the advent of today's immensely better and progressive understanding of molecular genetics, coupled with the small absolute numbers of childhood brain tumors.

Nevertheless, for general purposes, overall categories in children persist: astrocytomas (e.g., pilocytic astrocytoma, and diffuse astrocytomas, including diffuse midline glioma H3 K27M mutant) and other gliomas (e.g., ganglioglioma); embryonal tumors (e.g., medulloblastoma, atypical teratoid rhabdoid tumor, and pineoblastoma), ependymal tumors (e.g., ependymoma, subependymoma, and myxopapillary ependymoma), and germ cell tumors (germinoma and non-germinomatous germ cell tumor).

Pilocytic astrocytomas comprise about 15% of brain tumors among ages 0–19 years, while malignant gliomas, glioblastomas, and other astrocytomas account for another 22%.[2] Embryonal tumors, principally medulloblastoma, account for over 10% of childhood brain tumors. Embryonal tumors occur at a median age of 8 years. In particular, medulloblastoma is more common in males, except *SHH* subtype observed almost equally among male and female infants and also in young adults.[3] *MYC*-driven group 3 and neuronal group 4 medulloblastoma are far more common in boys, peak around the end of the first decade, and present very often with metastases. Ependymoma and germ cell tumors account for another 5% and 4%, respectively, of childhood brain tumors. Ependymomas are more common in males, with mean ages of presentation 5, 7.8, and 12.2 years for infratentorial, supratentorial, and spinal ependymoma, respectively.[4] Germ cell tumors occur more commonly in adolescence and young adult years, with higher incidence among Asians and Pacific Islanders. Males account for three-quarters of germ cell tumors and over 90% of those occurring at the pineal region.[5]

The broad categories of all brain tumors combined, as well as astrocytomas and other gliomas, medulloblastomas, ependymomas, and germ cell tumors will be used in this chapter. We will review here the patterns of incidence overall, and by time and space, before considering genetic, environmental, parental, and other risk factors.

2.2 GEOGRAPHICAL INCIDENCE OF BRAIN TUMORS

The incidence of childhood brain tumors displays marked variation across populations. This is demonstrated by data published by the International Agency for Research on Cancer (IARC).[6] Table 2.1 presents age-standardized rates (per 1 million children per year) from a selected representative set of population-based registries. The highest rates (>20 per million children per year) are evident in Europe, New Zealand (non-Maoris), Australia, North America, Japan, and Israel (Jews), with lowest rates in Eastern Europe, India, and Africa.[7] A recent study from the Central Brain Tumor Registry of the United States (CBTRUS)[2] reports the incidence of malignant brain tumors ages 0–19 years to be 3.5/1,000,000, and that of benign brain tumors as

Table 2.1 Incidence of childhood brain tumors: international comparisons – age-standardized rates per million

Registry	All central nervous system tumors
Denmark (1983–1991)	38.8
Australia (1982–1991)	29.6
Sweden (1983–1989)	41.0
USA, SEER, White (1998–1992)	31.8
UK, England and Wales (1981–1990)	27.0
Cali, Colombia (1982–1991)	16.8
Japan (1980–1992)	21.1
Estonia (1980–1989)	25.6
USA, SEER, Black (1983–1992)	27.4
Israel, Jews (1980–1989)	29.9
Bulgaria (1980–1989)	16.0
Bombay, India (1980–1992)	11.2
Israel, non-Jews (1980–1989)	18.1
Ibadan, Nigeria (1985–1992)	11.1

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.
Source: Based on data from Parkin DM, Kramarova GJ, Draper GJ, et al., eds. International incidence of childhood cancer, Vol. II. Lyon: IARC Scientific Publications, No. 144, 1998.[6]

2.4/1,000,000. One study from Scotland, a country which has universal health insurance, found increased risk of childhood brain tumors in areas with higher levels of affluence.[8] However, two other studies from England found no association between incidence and area-level socio-economic deprivation.[9,10] Geographical differences in incidence may reflect differences in genetic predisposition or exposure to putative etiological agents. It is also possible that at least some of the disparities may reflect differences in case ascertainment, especially in those countries that do not have universal health insurance.

2.3 TEMPORAL TRENDS IN THE INCIDENCE OF BRAIN TUMORS

Data from the US Surveillance, Epidemiology, and End Results (SEER) program showed a 35% rise in incidence from the mid-1970s to the mid-1990s. It has been suggested that this increase might be due to improved detection rather than a real increase.[11,12] However, another study from northwest England analyzed trends in the incidence of brain tumors from 1954 to 1998 and could not attribute increases in incidence (of pilocytic astrocytoma, primitive neuroectodermal tumors, and miscellaneous gliomas) to improvements in diagnosis.[13] A study from Sweden found increases in the incidence of astrocytoma during the period 1973–1992.[14] Another study from Sweden found increases in the incidence of CNS tumors during the period 1960–1998. Increases were seen for low-grade glioma/astrocytoma, benign brain tumors, and PNET/medulloblastoma. The authors suggested that changes in diagnostic criteria might have led to these increases.[15] More recently a study from Yorkshire analyzed data on CNS tumors in children and young adults during the period 1990–2001, but found only increases for young adults in "other CNS" tumors.[16] A study from Norway for the period 1970–1999 noted continued increases in those aged 0–4 years.[17] A report from the Automated Childhood Cancer Information System project of European children for the period 1978–1997 found increases in incidence in all regions of Europe, except the south. More rapid increases were noted in the east.[18] A study from northern England found significant increases in the incidence of childhood brain tumors during the period 1968–2005, due to increases in the incidence of astrocytoma.[19] A study from Sweden did not find any increases in the incidence of CNS tumors in Sweden during the period 1984–2005.[20] Increases in childhood brain tumors have been reported from Alberta, Canada, during the period from 1982 to 2004.[21] A study of US SEER data for the period 1973–2009 found that rates have remained stable during the last two decades.[22] However, by contrast, another recent study used data from the CBTRUS incorporating 47 sites from the National Program of Cancer Registries as well as five SEER sites and found an annual increase of childhood malignant brain tumors of 0.6% per year during the period 2004–2015.[2] Non-malignant childhood brain tumors increased 2.3% annually from 2004 to 2015, although this change was partially attributed to improved collection of all non-malignant cases as well as those radiographically diagnosed cases.

The overall evidence suggests that there has been a real, albeit small, increase in the incidence of childhood brain tumors in recent decades. This could suggest increased exposure to one or more environmental agents, or complex interactions of environment and genes. However, it is also possible that some of the increases are due to improvements in diagnostic techniques.

2.4 SPACE–TIME AND SPATIAL CLUSTERING IN THE INCIDENCE OF BRAIN TUMORS

2.4.1 Space–time Clustering

Space–time clustering occurs if excess case numbers are seen within small spatial locations at specific time points and which are not explainable as generalized excesses in the specific locations or times. Thus, space–time clustering is often described as "an irregular grouping of cases of any specified disease simultaneously in space and time." Such irregular occurrences could arise from the following possible scenarios:

1. A few "localized areas" with markedly increased incidence at distinct short time periods
2. Many "localized areas" with moderate increases in incidence at limited time periods
3. A few distinct short "periods of time" with markedly increased incidence at a limited number of "localized areas"
4. Many limited "periods of time" with modest increases in incidence at a limited number of "localized areas."

If certain types of environmental exposure (e.g., infections) are involved in the etiology of childhood brain tumors then the case distribution may manifest space–time clustering. It should be noted that this would occur only if the environmental exposure happened in small "epidemics" or if it had an effect on only a few susceptible individuals. If an environmental exposure was endemic or ubiquitous, then this would be expected to lead to a case distribution that was homogeneous without any manifestation of space–time clustering. In studies of incidence patterning, distributions of space and time may be allocated with respect to addresses and times of residence at birth or diagnosis. Such studies are enabled via consistent and reliable population-based data over a reasonably large geographical area and time frame. If the critical environmental exposure occurred during the prenatal period or around the time of birth, then there could be a manifestation of space–time clustering based on date and location of birth. Conversely if the critical environmental exposure occurred around the time of diagnosis, then there could be a manifestation of space–time clustering based on date and location of diagnosis. This scenario could also occur if there is a fairly constant time between the initiating exposure and subsequent diagnosis. There is another possibility. If there is much residential migration between birth and diagnosis, space–time clustering could be manifest based on diagnosis time and birth location. However, this would occur only if the initial exposure was at the location of birth and there was a constant time from that exposure and subsequent diagnosis. Various statistical methods have been used to study space–time clustering.[23,24] Earlier methods have relied on arbitrary choices for definitions of "close in time" and "close in space." The method of Diggle et al.[24] circumvents this issue. Statistically significant space–time clustering is indicative of an environmental component to etiology, such as an infectious exposure.

Studies of space–time clustering are presented in Table 2.2. Three studies from the UK[25–27] found evidence of space–time clustering based on time and place of diagnosis (the environmental exposure occurring close to diagnosis). One study from the UK[28] showed space–time clustering based on time and place of birth (environmental exposure occurring in utero or around the time of birth) and also based on place of birth and time of diagnosis (environmental exposure around the place of birth with a constant interval between the initiating exposure and subsequent diagnosis). There were differences between analyses in the specific subdiagnostic groups that displayed space–time clustering between each other. Further, there was evidence of cross-space–time clustering between cases of CNS tumor and leukemia based on time and place of diagnosis,[29] between cases of astrocytoma and acute lymphoblastic leukemia based on time and place of birth,[29] between cases of intracranial and intraspinal embryonal tumors and

Table 2.2 Space–time clustering of childhood brain tumors

Study	Country	Age (years)	Time period	Findings
Based on time of diagnosis and place of diagnosis				
Hjalmars et al. (1999)[14]	Sweden	0–15 years	1973–1992	No significant clustering
McNally et al. (2002)[25]	Northwest England	0–14 years	1954–1998	Significant clustering of astrocytoma and ependymoma
McNally et al. (2005)[29]	Northwest England	0–14 years	1954–1998	Significant cross-clustering between cases of CNS tumor and leukemia
McNally et al. (2006)[26]	Great Britain	0–14 years	1969–1993	Marginally significant clustering of astrocytoma ($P = 0.06$)
McNally et al. (2012)[27]	Yorkshire, UK	0–14 years	1974–2006	Significant clustering of primitive neuroectodermal tumors
Statistically significant based on time of birth and place of birth				
McNally et al. (2005)[29]	Northwest England	0–14 years	1954–1998	Significant cross-clustering between cases of acute lymphoblastic leukemia and astrocytoma
McNally et al. (2009)[28]	Great Britain	0–14 years	1969–1993	Significant clustering of all CNS tumors together, but not astrocytoma
Statistically significant based on time of diagnosis and place of birth				
McNally et al. (2009)[28]	Great Britain	0–14 years	1969–1993	Marginally significant clustering of all CNS tumors together and, separately, astrocytoma ($P = 0.06$)
McNally et al. (2014)[30]	Great Britain	0–14 years	1969–1993	Significant cross-clustering between cases of Hodgkin lymphoma and intracranial and intraspinal embryonal tumors and between non-Hodgkin lymphoma and astrocytoma

Abbreviation: CNS, central nervous system.

Hodgkin lymphoma, and between cases of astrocytoma and non-Hodgkin lymphoma based on place of birth and time of diagnosis.[30] Taken together, these studies show some evidence for the involvement of one or more transient, spatially heterogeneous, environmental exposures in the etiology of childhood brain tumors. Plausible candidates could include infectious agents or certain atmospheric pollutants.

2.4.2 Spatial Clustering

Spatial clustering is said to be "an irregular grouping in any specified disease in space." Such clustering would be a general occurrence and would not be limited to one particular small area. Such a scenario could happen if there are a few areas with markedly increased incidence or many more areas with more modest increases in incidence. A finding of spatial clustering could be indicative of the involvement of a spatially heterogeneous environmental factor in etiology. A number of statistical methods have been used to test for spatial clustering.[31–33] The analysis of spatial clustering is dependent on accurate population data by age and sex for small geographical areas. Inaccurate population data could lead to an inflation or deflation of a clustering effect. Underestimation of a population count within a small geographical area may lead to an excess that is not real. Conversely, an overestimation of a similar population count may result in a deficit that is not real.

There have been only a few studies that have examined spatial clustering of childhood brain tumors. A study which analyzed cases from Yorkshire, UK, diagnosed during the period 1974–1986 found no localized clustering. However, mapping indicated high risk in a particular section of the county.[34] A regional study from northwest England analyzed all cases of brain tumor in those aged 0–14 years and diagnosed during 1976–2000, but found no evidence of spatial clustering.[10] A national study analyzed all cases of childhood brain tumor from the whole of Great Britain, diagnosed during the period 1969–1993, and found no evidence of spatial clustering.[35] Taken together, the lack of spatial clustering suggests there is little evidence for sustained localized clustering of childhood brain tumors. Thus, any putative etiological agents are more likely to be transient.

2.4.3 Seasonal Variation

Seasonal variation in the incidence of brain tumors might also provide evidence for an environmental exposure etiology, such as infection. Overall, seasonal patterns have not been detected in the birth season or occurrence season for most children.[10,36,37] In one prefecture of Japan, Makino et al.[37] did detect a modest incidence peak in germ cell tumors among children born during the winter. A statistically significant peak in incidence of medulloblastoma diagnosis was noted in October for children captured by CBTRUS from 1995 to 2001.[38]

2.4.4 Occupational Clusters

The finding of an occupational cluster would suggest the involvement of an environmental exposure in etiology. One study found a cluster of brain tumors in six unrelated children (observed/expected = 70, $P < 0.001$), whose parents worked in the same electronics factory in Ohio.[39]

2.5 GENETIC AND FAMILIAL RISK FACTORS

For many years, the occurrence of childhood brain tumors was viewed as sporadic in regard to genetic predisposition. Previously 2% or less of tumors were considered to be genetic in origin,[40] while a familial predisposition to cancers was still recognized.[41] Syndromes with known chromosomal defects, such as neurofibromatosis 1 and 2 and tuberous sclerosis, have long been known to be associated with gliomas, particularly astrocytomas. However, an explosion in molecular genetics over the past decade[42] has transformed our thinking such that genetic predisposition is now recognized in at least 8% of childhood cancer[43] and 5% or far more of childhood brain tumors.[44] Germline mutations in *INI1*,[45] *TP53*,[46] *DICER1*,[47] *SUFU*, and *PTCH1*[44] are now recognized as common in atypical teratoid rhabdoid tumor, choroid plexus carcinoma, pineoblastoma, and SHH-subgroup medulloblastoma, respectively. Other germline mutations in genes such as *APC*, *CTNNB1*, *PALB2*, and *BRCA2* also clearly play a role in childhood brain tumor predisposition. A current understanding of genetic predispositions to brain tumors is provided in Table 2.3.

2.6 ENVIRONMENTAL RISK FACTORS

2.6.1 Ionizing Radiation

There are a number of possible sources of exposure to ionizing radiation. These include residential exposure (background radon or gamma radiation and man-made sources), occupational exposure (of the parent), parental preconception or prenatal diagnostic exposure, and direct diagnostic or therapeutic exposure of the child. A systematic review found no evidence that either pre- or postnatal exposure to X-rays confers increased risk of childhood brain tumors.[48] A case-control study from Australia found only increased odds ratios for high-grade gliomas. However, numbers were small and so this may have been a chance finding.[49] A recent large cohort study from Australia assessed cancer risk in children and adolescents following exposure to low-dose ionizing radiation from diagnostic computed tomography (CT) scans and found twofold increased risk for brain tumors with a dose–response relationship.[50] Overall, the only positive risk factors are associated with CT scans (Table 2.4). Therapeutic cranial irradiation has been well established to lead to brain tumors, particularly high-grade cancers and meningiomas.[51]

2.6.2 Mobile Telephones

A multicenter case-control study from four European countries (Denmark, Sweden, Norway, and Switzerland) found no association between mobile phone use and risk of brain tumors in children and adolescents. There was no association with longevity of use, nor with those areas of the brain that received the highest levels of exposure (Table 2.5).[52]

Table 2.3 Childhood brain tumors with known genetic predisposition syndromes or germline gene defects

Tumor	Predisposition mutation or syndrome
Atypical teratoid rhabdoid tumor (ATRT)	*SMARCB1/INI1* germline mutations
Choroid plexus carcinoma	Germline P53 mutation (Li–Fraumeni syndrome)
Dysplastic cerebellar gangliocytoma	Cowden syndrome (*PTEN* mutation)
Ependymoma	Neurofibromatosis 2, multiple endocrine neoplasia type 1, and Li–Fraumeni and Turcot syndromes
Germ cell tumors	Klinefelter and Down syndromes
Hemangioblastoma	von Hippel–Lindau syndrome
High-grade astrocytoma	Constitutional mismatch repair deficiency (*MLH1*, *MSH2*, *MSH6*, and *PMS2* mutations); Li–Fraumeni and Turcot syndromes
Low-grade astrocytoma	Neurofibromatosis 1, tuberous sclerosis
Meningioma	Neurofibromatosis 2
Medulloblastoma	*SUFU* and *PTCH1* germline mutations (Gorlin syndrome); Li–Fraumeni, Turcot, ataxia telangiectasia (ATM), Nijmegen breakage, Rubenstein–Taybi, and Coffin–Siris syndromes
Pineoblastoma	*DICER1* germline mutations
Schwannoma	Neurofibromatosis 2
Subependymal giant cell astrocytoma (SEGA)	Tuberous sclerosis

Table 2.4 Ionizing radiation and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% confidence interval)	
Schulze-Rath et al. (2008)[48]	Brain tumors	Various	Systematic review	Pre- or postnatal X-rays	No significant effect of pre- and postnatal X-rays on risk of childhood brain tumors
Milne et al. (2014)[49]	Brain tumors	Australia	Case-control	Childhood or parental pre-pregnancy radiological procedures	No evidence of positive associations between risk of brain tumors overall and childhood or parental pre-pregnancy radiological procedures Increased odds ratios for high-grade gliomas associated with childhood radiological procedures (based on small numbers so may be due to chance)
Matthews et al. (2013)[50]	Brain tumors	Australia	Cohort	Computed tomography scans	Incidence rate ratio = 2.13 (1.88–2.41) with dose–response relation

Table 2.5 Mobile telephones and the risk of childhood brain tumors

Study	disease	Place	Study design	Exposure & risk estimate (95% CI)	
Aydin et al. (2011)[52]	Brain tumors	Multicenter: Denmark, Sweden, Norway, and Switzerland	Case-control	Mobile phone use	Regular use of mobile phones OR = 1.36, 95% CI 0.92–2.02 Children who started to use mobile phones at least 5 years ago compared with those who had never regularly used mobile phones OR = 1.26, 95% CI 0.70–2.28 No increased risk for brain areas receiving the highest amount of exposure

Abbreviations: CI, confidence interval; OR, odds ratio.

However, the authors commented that further research is required.[53]

2.6.3 Electromagnetic Fields

Despite early, limited reports of childhood leukemia clustering near power lines, there is currently little evidence to support any association between residential electromagnetic fields and childhood brain tumors. Saito et al.[54] reported a positive association between high-level exposure (above 4 μT) and the risk of brain tumors, but that was based on 3 cases and 1 control at that level of exposure and an imprecise odds ratio of 10.9 (95% confidence interval 1.05–113). All other investigations, whether using metrics such as wire configuration, spot electrical field measurement, or personal report of electric appliance or heat usage, have not found any evidence for an increase in childhood brain cancer risk paired with electromagnetic fields .[55–59]

2.7 RISK FROM PARENTAL OCCUPATIONAL AND SOCIOECONOMIC EXPOSURES

Increased risk of childhood brain tumors has been associated with a number of parental occupations in some, but not all, studies, including electricians, electronics, nurses, agriculture, painters, drivers, cooks, mechanics, and textile workers.[60–65] Specific exposures include pesticides, herbicides, fungicides, and paints.[66–68] One study found raised risk of astrocytoma and other gliomas for high paternal occupational social contact.[69] Another study found higher risk of glioma associated with higher socioeconomic position.[70] By contrast, other studies found no associations (Table 2.6). Overall, there is evidence of consistent associations with certain occupations, reflecting possible exposure to specific putative etiological agents.

2.7.1 Parental Chemical Exposures

A case-control study from California and Washington state found an increased risk of astroglial tumors associated with both fathers and mothers working in the chemical industry.[62] Another multicenter, case-control study from three European countries (Italy, France, and Spain) considered specific chemical exposures and found the following increased risks: PNETs with paternal exposure to polycyclic aromatic hydrocarbons, and both astroglial tumors and PNETs with maternal exposure to solvents (Table 2.7).[61]

2.7.2 Parental Smoking (Pre- and Postnatal)

There have been three recent studies and three meta-analyses of older studies (Table 2.8) on parental smoking as a risk factor. Two of the more recent studies showed some limited associations between maternal smoking during pregnancy and increased risk of glioma or astrocytoma.[71,72] The third, recent, multicenter case-control study found no association.[73] One of the three meta-analyses of older studies found an association between paternal smoking during pregnancy and increased risk of childhood brain tumors.[74] The second meta-analysis found no association between maternal smoking during pregnancy and risk of brain tumors.[75] The third meta-analysis found little or no association between maternal or paternal smoking before or during pregnancy and risk of childhood brain tumors.[76] Overall, the evidence from both recent and older studies does not support an association between parental smoking and increased risk of childhood brain tumors.[77–95]

2.7.3 Parental Alcohol Consumption

There is little evidence to suggest that there is any link between maternal prenatal alcohol consumption and risk of childhood brain tumors.[78,85,96–98] Two studies have indicated a link between paternal preconception use of hard liquor or spirits and increased risk of childhood brain tumors (Table 2.9).[85,98] However, this finding is somewhat tentative and requires confirmation in future studies.

2.7.4 Parental Intake of Vitamins and Folic Acid Before and During Pregnancy

A number of case-control studies and a cohort study have shown a protective effect of vitamin supplementation and folic acid intake both before and during pregnancy. Specific vitamins include A, B_6, B_{12}, and C.[99–110] A meta-analysis of seven studies found a protective effect of maternal prenatal multivitamin supplementation.[111] A case-control study from Australia found an increased protective effect of maternal folic acid intake during pregnancy if the child, mother, or father had the *MTRR* 66GG genotype.[112] The overall evidence suggests that intake of folic acid and vitamins during pregnancy confers protection against developing brain tumors (Table 2.10).

2.7.5 Incense Burning During Pregnancy

Incense is a nitrosamine-containing substance and has been hypothesized to be a risk for childhood brain tumors. Only one of three case-control studies found an association between burning incense during pregnancy and risk of childhood brain tumors (Table 2.11). Thus, there is only very limited evidence that suggests a possible link.

2.7.6 Maternal Use of Face Make-up During Pregnancy

A case-control study from the USA found an increased risk of childhood brain tumors (Table 2.12). This has been explained by the constituent N-nitroso compounds.[113]

2.7.7 Maternal Hair Dye Use During Pregnancy

Two case-control studies have not detected an association between risk for childhood brain tumor and use of hair dyes during pregnancy.[114,115] In addition, Efird et al.[114] did not find convincing evidence for risk of childhood brain tumors associated with exposures to any beauty products in the 5 years preceding a child's birth.

2.8 OTHER RISK FACTORS

2.8.1 Breastfeeding

Case-control studies have not revealed any association between breastfeeding and risk of childhood brain tumors (Table 2.13).[78,116,117]

Table 2.6 Parental occupational and socioeconomic exposures and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Kuijten et al. (1992)[60]	Astrocytoma	USA	Case-control	Significant association: fathers' occupation as electrical or electronic repairmen Significant association: mothers employed as nurses
Cordier et al. (1997)[61]	Brain tumors	Italy/France/ Spain	Case-control	All brain tumors: father worked in agriculture: OR = 2.5, 95% CI 1.0–4.7 Primitive neuroectodermal tumors: father worked in motor vehicle-related occupation: OR = 2.7, 95% CI 1.1–6.6 Astroglial tumors: mother worked in health services: OR = 2.2, 95% CI 1.0–4.9
Fear et al. (1998)[154]	Brain tumors	UK	Record linkage	Paternal employment in agriculture – no association
McKean-Cowdin et al. (1998)[62]	Brain tumors	California/ Washington states	Case-control	Any brain tumor – fathers employed as electrical workers: OR = 2.3, 95% CI 1.3–4.0
Sorahan et al. (1999[155]	Brain tumors	UK	Case-control	Maternal occupational exposure to electromagnetic field – no associations
Feychting et al. (2000)[156]	Brain tumors	Sweden	Cohort	Parental occupational exposure to magnetic fields: RR = 0.5, 95% CI 0.3–1.0
Feychting et al. (2001)[66]	CNS tumors	Sweden	Cohort	Paternal occupational exposure to pesticides: RR = 2.36, 95% CI 1.27–4.39 Paternal occupation as painter: RR = 3.65, 95% CI 1.71–7.80
Cordier et al. (2001)[63]	Brain tumors	Seven countries	Case-control	All brain tumors – agriculture – increased risk Other glial tumors – agriculture – increased risk All brain tumors – paternal occupation as electrician – increased risk PNET – paternal occupation as electrician – increased risk All brain tumors children <5 years – maternal occupation as electrician – increased risk PNET children <5 years – maternal occupation as electrician – increased risk All brain tumors – paternal occupation as driver or mechanic – increased risk Astroglial tumors – paternal occupation as driver or mechanic – increased risk All brain tumors – maternal occupation related to motor vehicles – increased risk Astroglial tumors – maternal occupation related to motor vehicles – increased risk
Mutanen et al. (2001)[64]	Brain tumors	Sweden	Registry study	Brain cancers – children of female cooks
Van Wijngaarden et al. (2003)[67]	Brain tumors	USA and Canada	Case-control	Astrocytoma – paternal exposure to pesticides: OR = 1.4–1.6 PNET – paternal exposure to herbicides – OR = 1.5 Astrocytoma – maternal exposure to insecticides, herbicides and non-agricultural fungicides OR = 1.3–1.6

(*continued*)

Table 2.6 Parental occupational and socioeconomic exposures and the risk of childhood brain tumors (cont.)

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Ali et al. (2004)[65]	Brain tumors	Taiwan	Case-control	*Preconception, perinatal, and postnatal periods* Mothers worked in electronic parts and components manufacturing: OR = 13.78, 95% CI 1.47–129.0 Mothers worked as textile and garment workers: OR = 7.25, 95% CI 1.42–37.0 Mothers worked with certain electronic components: OR = 28.67, 95% CI 1.42–37.0 *Preconception period* Mothers worked in electronic parts and components manufacturing: OR = 11.81, 95% CI 1.20–116.3 Mothers worked as textile and garment workers: OR = 7.25, 95% CI 1.18–31.0
Rosso et al. (2008)[68]	Medulloblastoma and PNET	USA	Case-control	*Fathers' exposure* Lawn care with pesticides – during pregnancy: OR = 1.6, 95% CI 1.0–2.5 Lawn care with pesticides – after birth: OR = 1.8, 95% CI 1.2–2.8 Stripping paint —during pregnancy: OR = 1.4, 95% CI 0.8–2.6 Stripping paint—after birth: OR = 1.4, 95% CI 0.7–2.6
Mazumdar et al. (2008)[157]	Brain tumors	Taiwan	Case-control	No association with parental occupation
Keegan et al. (2013)[69]	CNS tumors	Great Britain	Case-control	Little evidence linking paternal occupation to CNS risk Astrocytoma and other gliomas—risk raised for high paternal occupational social contact
Khanolkar et al. (2016)[70]	Brain tumors	Sweden	Cohort	Glioma—consistent association with higher socioeconomic position

Abbreviations: CI, confidence interval; CNS, central nervous system; OR, odds ratio; PNET, primitive neuroectodermal tumor; RR, relative risk.

Table 2.7 Chemical exposures and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Cordier et al. (1997)[61]	Brain tumors	Italy/France/ Spain	Case-control	Primitive neuroectodermal tumors: paternal exposure to PAHs: OR = 2.0, 95% CI 1.0–4.0 Astroglial tumors: maternal exposure to solvents: OR = 2.3, 95% CI 0.9–5.8 Primitive neuroectodermal tumors: maternal exposure to solvents: OR = 3.2, 95% CI 1.0–10.3
McKean-Cowdin et al. (1998)[62]	Brain tumors	California/ Washington states	Case-control	Astroglial tumors – fathers worked in chemical industry: OR = 2.1, 95% CI 1.1–3.9 Mothers worked in chemical industry: OR = 3.3, 95% CI 1.4–7.7

Abbreviations: CI, confidence interval; OR, odds ratio; PAHs, polycyclic aromatic hydrocarbons.

Table 2.8 Parental smoking and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Huncharek et al. (2001)[74]	all CNS	Various	Meta analysis	Paternal smoking during pregnancy—RR = 1.29 (95% CI 1.07–1.53)
Huncharek et al. (2002)[75]	all CNS	Various	Meta-analysis of 6566 subjects from 12 studies	Maternal smoking during pregnancy—RR = 1.05 (95% CI 0.90–1.21)
Huang et al. (2014)[76]	all CNS	Various	Meta-analysis of 17 studies	Maternal smoking during pregnancy—RR = 0.96 (95% CI 0.86–1.07) Paternal smoking during pregnancy—RR = 1.09 (95% CI 0.97–1.22) Maternal smoking before pregnancy—RR = 0.93 (95% CI 0.85–1.00) Paternal smoking before pregnancy—RR = 1.09 (95% CI 1.00–1.20)
Heck et al. (2016)[71]	gliomas	California	Case-control	Maternal smoking during pregnancy—OR = 1.8 (95% CI 1.0–3.4)
Tettamanti et al. (2016)[72]	brain tumors	Sweden	Cohort	Maternal smoking during pregnancy—all childhood brain tumors among male children—RR = 1.50 (95% CI 0.96–2.34) Astrocytoma among male children—RR = 2.00 (95% CI 1.02–3.91) Astrocytoma among female children—RR = 1.80 (95% CI 0.85–3.82)
Vienneau et al. (2016)[73]		Multinational (Denmark, Sweden, Norway, Switzerland)	Case-control	Maternal smoking during pregnancy—no association

Abbreviations: CI, confidence interval; CNS, central nervous system; OR, odds ratio; RR, relative risk.

Table 2.9 Parental alcohol consumption and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Kuijten et al. (1990)[96]	Astrocytoma	USA	Case-control	Gestational exposure to alcohol—OR = 1.4 (95% CI 0.8–2.5)
Hu et al. (2000)[85]	Brain tumors	China	Case-control	Paternal use of hard liquor ≤15 years—OR = 3.72 (95% CI 1.92–7.26) Paternal use of hard liquor ≥16 years—OR = 4.06 (95% CI 1.09–15.21)
Schuz et al. (2001)[78]	CNS tumors	Germany	Case-control	Maternal alcohol consumption—no association
Milne et al. (2013)[98]	Brain tumors	Australia	Case-control	Maternal alcohol consumption—no association Paternal consumption of any spirits—OR = 1.46 (95% CI 1.07–2.00)

Abbreviations: CI, confidence interval; OR, odds ratio.

2.8.2 Diet and the Risk of Childhood Brain Tumors

Protective effects of maternal consumption during pregnancy have been seen for consumption of fresh vegetables, fruits and fruit juices, nitrate, iron, and calcium.[99,118] Consumption of fruit by children aged <1 year of age has also been shown to have a protective effect.[119] By contrast, maternal consumption of processed meats, nitrite, potassium, tea, and coffee has demonstrated increased risks in some case-control studies.[120–124] A meta-analysis of six studies found increased risk associated with maternal consumption of cured meat and hot dogs during pregnancy.[125] These studies show possible associations between dietary factors and risk of brain tumors (Table 2.14).

Table 2.10 Maternal intake of vitamins, folic acid, and iron and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Bunin et al. (1993)[99]	Primitive neuroectodermal tumors	USA	Case-control	Vitamin A during pregnancy: OR = 0.59; *P* = 0.03 Vitamin C during pregnancy: OR = 0.42; *P* = 0.009 Folate: OR = 0.38; *P* = 0.005
Cordier et al (2004)[91]	Brain tumors	France	Case-control	Vitamin supplements during childhood—decreased risk
Preston-Martin et al. (1998)[101–103]	Brain tumors	International	Case-control	Maternal vitamin supplementation for two trimesters: OR = 0.7; 95% CI 0.5–0.9
Bunin et al. (2006)[100]	Medulloblastoma/primitive neuroectodermal tumors of brain	USA and Canada	Case-control	Multivitamins during periconception period: OR = 0.7; 95% CI 0.4–1.0 Highest quartile of folate intake from food and supplements: OR = 0.5;95% CI 0.3–0.9
Goh et al. (2007)[158]	Brain tumors	Various	Meta-analysis	Prenatal maternal multivitamins: OR = 0.73; 95% CI 0.60–0.88
Grupp et al. (2011)[104]	Brain tumors	Canada	Cohort	Folic acid flour fortification; no significant change in pre-fortification vs. post-fortification periods
Stalberg et al. (2010)[105]	Brain tumors	Sweden	Case-control	Prenatal exposure to folic acid: OR = 0.6; 95% CI 0.3–1.1
Milne et al. (2012)[106]	Brain tumors	Australia	Case-control	Maternal use of folic acid without iron before pregnancy: OR = 0.68; 95% CI 0.46–1.00 Maternal use of vitamins B_6, B_{12}, C, or A before pregnancy: OR = 0.55; 95% CI 0.32–0.93 Any maternal vitamin use before pregnancy: OR = 0.68; 95% CI 0.46–1.01
Greenop et (2014)[87]	Brain tumors	Australia	Case-control	Maternal gestational intake—highest vs. lowest tertile of folate intake: OR = 0.70; 95% CI 0.48–1.02 B_6/B_{12} supplementation: OR = 0.51; 95% CI 0.25–1.06
Greenop et al. (2015)[108]	Brain tumors	Australia	Case-control	Paternal preconception intake—folate, B_6—no association B_{12}—highest vs. lowest tertile: OR = 1.74; 95% CI 1.14–2.66
Greenop et al. (2015)[109]	Brain tumors	Australia	Case-control	Folate—highest vs. lowest tertile: OR = 0.63; 95% CI 0.41–0.97 Low-grade gliomas: OR = 0.52; 95% CI 0.29–0.92 Vitamin B_6—no association Vitamin B_{12}—no association
Greenop et al. (2015)[112]	Brain tumors	Australia	Case-control	Maternal pregnancy folic acid and child, mother, or father had *MTRR* 66GG genotype—negative association

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 2.11 Incense burning during pregnancy and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)	
Preston-Martin et al. (1982, 1984)[113,159]	Brain tumors	Los Angeles County	Case-control	Incense burning	OR = 3.3; *P* = 0.005
McCredie et al. (1994)[82]	Brain tumors	New South Wales	Case-control	Incense burning	No association
Bunin et al. (1994)[118]	Astrocytic glioma and primitive neuroectodermal tumor of the brain	USA	Case-control	Incense burning	No association for either astrocytic glioma or primitive neuroectodermal tumors

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 2.12 Maternal use of face make-up and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)	
Preston-Martin et al. (1982)[113]	Brain tumors	USA	Case-control	Maternal face make-up	OR = 1.6; *P* = 0.02

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 2.13 Breastfeeding and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Schuz et al. (2001)[78]	CNS tumors	Germany	Case-control	During of breastfeeding—no association
Harding et al. (2007)[116]	CNS tumors	UK	Case-control	Breastfeeding: OR = 1.01; 95% CI 0.85–1.21
Greenop et al. (2015)[117]	Brain tumors	Australia	Case-control	Breastfeeding—no association

Abbreviations: CI, confidence interval; CNS, central nervous system; OR, odds ratio.

2.8.3 Drinking Water

There is a limited number of studies that show a possible, but tentative, link between nitrate in drinking water and increased risk of childhood brain tumors[126–128] One study from California and Washington state showed conflicting evidence. Overall, there was no association with nitrate. However, there was increased risk for childhood brain tumors in the offspring of women who only used well water.[126] Another multicenter, international case-control study found no overall association. However, increased risk of astrocytoma was associated with higher levels of nitrate in the drinking water.[127] Another study from Taiwan found increased risk of brain tumors in areas with high nitrate exposure in the water.[128] Overall, studies show a possible association with nitrate in drinking water and increased risk of childhood brain tumors (Table 2.15).

2.8.4 Infections

Evidence for a link between antecedent infections and childhood brain tumors is minimal to date. One retrospective cohort study found no association with measures of community infection,[129] while another case-control study did not observe an association with reported repeated infections or exposure to day care, but did note a small protective effect from visits to farms and pet ownership.[130] Other case-control studies have noted limited evidence for the role of prenatal and neonatal infections,[131] weakly elevated risk after maternal reported exposure to several potential proxies of infection,[132] and no association with number of social contacts, but more sick days among cases with infections in the first 6 years of life.[133]

2.8.5 Parental Age and Medical History

There is modest support from retrospective studies that advancing maternal age[134,135] and paternal age[136,137] increase the risk of brain tumors in offspring. Such evidence would support the hypothesis that accumulation of germline mutations among parents over time is a potential cause for a child's brain tumor. However, these studies have often simultaneously examined all childhood cancer types at once, rather than setting out a priori to examine brain tumor occurrence.

As far as maternal reproductive history, including factors such as birth order, fetal loss, and use of fertility drugs, pooled analysis of the French ESTELLE and ESCALE studies did not find any association with childhood brain tumors.[138] However, that same investigation also did not find a relationship with birth weight or congenital anomalies, in contrast to multiple other studies (see below).

Table 2.14 Diet and risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Bunin et al. (1993)[99]	Primitive neuroectodermal brain tumors	USA	Case-control	Fresh vegetables—OR for highest quartile relative to lowest = 0.37—*P* for trend = 0.005 Fruits and fruit juices—OR = 0.28; *P* = 0.003 Nitrate—OR = 0.44; *P* = 0.002 Nitrosamine—OR = 1.65; *P* = 0.15 (non-significant trend) Iron—OR = 0.43; *P* = 0.004 Calcium—OR = 0.42; *P* = 0.05
McCredie et al. (1994)[119]	Brain tumors	New South Wales	Case-control	Consumption of fruit by the child <1 year of age—protective effect
Bunin et al. (1994)[120]	Astrocytoma	USA	Case-control	Consumption of cured meats (containing preformed nitrosamines): OR = 1.7; *P* = 0.10 Nitrosamine: OR = 0.8; *P* = 0.60 Nitrite: OR = 1.3; *P* = 0.54 Nitrate: OR = 0.7; *P* = 0.43 Iron supplements: OR = 0.5; 95% CI 0.3–0.8
Preston-Martin et al. (1996)[55]	Brain tumors	USA	Case-control	Maternal consumption during pregnancy of processed meats for eating at least twice a day compared to not eating: OR = 2.1; 95% CI 1.3–3.2; *P* = 0.003 Increasing risk with increasing average daily intake of cured meats or nitrite from cured meats: *P* < 0.005
Lubin et al. (2000)[160]	Brain tumors	Israel	Case-control	Vegetable fat in the child's diet—OR = 1.36; 95% CI 1.06–1.73 Potassium intake during gestation—OR = 1.44; 95% CI 1.04–1.99
Pogoda et al. (2001)[122]	Brain tumors	USA	Case-control	Moderate increase in brain tumor risk in offspring of mothers with relatively low levels of nitrite consumption from cured meats during pregnancy Two- to threefold increased risk in offspring of mothers who consumed 3 mg/day nitrite from cured meats
Huncharek et al. (2004)[125]	Brain tumors	Various (six studies)	Meta-analysis	Maternal cured meat consumption during pregnancy: RR = 1.68; 95% CI 1.30–2.17 Hot dog consumption: RR = 1.44; 95% CI 1.06–1.66
Bunin et al. (2005)[161]	Medulloblastoma/PNET	USA	Case-control	Fruits/juices: OR = 0.6; 95% CI 0.3–1.1 Vegetables—no association Cured meats—no association Non-fresh peaches/similar fruits: OR = 0.5; 95% CI 0.3–0.8 Non-chocolate candy: OR = 1.7; 95% CI 1.0–3.0 French fries: OR = 2.4; 95% CI 1.2–4.9 Chilli peppers: OR = 1.8; 95% CI 1.0, 3.0

(*continued*)

Table 2.14 Diet and risk of childhood brain tumors (cont.)

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Pogoda et al. (2009)[123]	Brain tumors	Seven countries	Case-control	*Increased risk* Cured meats and astrocytomas: OR = 1.8–2.5; *P* for trend ≤0.03 Cured meats and ependymomas: OR = 2.0; 95% CI 0.4–2.9; *P* for trend = 0.03 Oil products and medulloblastoma: OR = 1.5; 96% CI 1.0–2.2; *P* for trend = 0.005 *Decreased risk* Cruciferous vegetables and anaplastic astrocytomas: OR = 0.4; 95% CI 0.3–0.7; *P* for trend <0.0001 Fresh fish and astroglial tumors: OR = 0.6; 95% CI 0.5–0.9; *P* for trend = 0.008
Greenop et al. (2014)[87]	Brain tumors	Australia	Case-control	Gestational consumption of any coffee during pregnancy: OR = 1.23; 95% CI 0.92–1.64 Gestational consumption of any tea during pregnancy: OR = 1.00; 95% CI 0.74–1.36 Children <5 years Any coffee consumption during pregnancy: OR = 1.76; 95% CI 1.09–2.84 ≥2 cups per day during pregnancy: OR = 2.52; 95% CI 1.26–5.04

Abbreviations: CI, confidence interval; OR, odds ratio; PNET, primitive neuroectodermal tumor; RR, relative risk.

Table 2.15 Drinking water and the risk of childhood brain tumors

Study	Disease	Place	Study design	Exposure & risk estimate (95% CI)
Mueller et al. (2001)[126]	Brain tumors	California and Washington state	Case-control	Overall—no association Western Washington among offspring of women who relied exclusively on well water: OR = 2.6 (95% CI 1.3–5.2) Los Angeles County: OR = 0.2 (95% CI 0.1–0.8) Presence of nitrate: OR = 1.1 (95% CI 0.7–2.0)
Mueller et al. (2004)[127]	Brain tumors	Multicenter (five countries)	Case-control	All brain tumors—no association with increasing nitrate levels Astrocytoma: OR = 4.3 (95% CI 1.4–12.6) for nitrite levels of 1–<5 mg/L OR = 5.7 (95% CI 1.2–27.2) for nitrite levels of ≥5 mg/L
Weng et al. (2011)[128]	Brain tumors	Taiwan	Case-control	Residence in municipalities with nitrate exposure >0.31 ppm: OR = 1.4 (95% CI 1.07–1.84)

Abbreviations: CI, confidence interval; OR, odds ratio.

Other investigations[139,140] have not identified a positive relationship between occurrence of childhood brain tumors and maternal age, fetal loss, birth order, or multiple births. The SEARCH international case-control study did not find any significant associations between maternal intake of medication containing nitrosatable amines or amides and childhood brain tumors.[141]

2.8.6 Birth Weight

There have been fairly convincing reports that increased birth weight, usually >4,000 g, elevates risk of childhood brain tumors, especially astrocytomas. Two case-control studies[87,138] could not detect an association between childhood brain tumors and birth weight. However, three other case-control studies[142–144] all identified significant relationships between astrocytomas or high-grade glioma and birth weight. Furthermore, two meta-analyses[145,146] have shown associations between increased birth weight and brain tumors combined, astrocytoma and embryonal tumors or medulloblastoma, but not ependymoma. Combined, these studies point to a potential overgrowth syndrome in childhood brain tumors that could hypothetically arise from dysregulated developmental genes or proto-oncogenes.

2.8.7 Congenital Anomalies and Birth Defects

Multiple studies have identified that congenital anomalies are associated with an increased risk of cancer, including brain tumors, that continues until early adulthood.[147] Risk estimates have ranged from 1.0 to 4.7. Even once children with known chromosomal defects are excluded, studied in a large cohort from California, children with congenital anomalies have a 1.8-fold risk of brain tumors, with the risks significantly increased in medulloblastoma and other embryonal tumors, along with germ cell tumors.[148] The risk of a childhood brain tumor in this same cohort is further compounded among mothers with more than two fetal losses after 20 weeks' gestation.[149] Furthermore, when that cohort is extended to young adults age 15–25, the association with brain tumors and birth defects disappears during those years.[150] This observation indicates that adolescent and young adult brain tumors are likely distinctly different from those that are diagnosed in children, and that childhood brain tumors may relate to aberrant developmental genes associated with congenital anomalies.

2.8.8 Head Injury and Epilepsy

Evidence that traumatic brain injury leads to a childhood brain tumor is weak[151] and likely subject to recall bias, since parents of cases are more likely than controls to remember falls. Further, the relationship is likely also confounded by the fact that brain tumors make children more ataxic and likely to fall.

Likewise, seizures are strongly associated with risk of childhood brain tumors, but such epilepsy is often due to occult tumors.[152] Two case-control studies have yielded inconsistent results regarding whether family history of seizures is associated with childhood brain tumors.[82,153] A positive result could potentially reflect a family-wide genetic susceptibility to brain dysplasia.

2.9 CONCLUSION

Despite substantial research and recent advances in understanding the molecular biology of childhood brain tumors, the causes of childhood brain tumors remain largely unknown. Known risk factors of cranial irradiation and genetic predisposition syndromes today explain far less than a quarter of incident childhood brain tumors. Future epidemiologic research will need to address new tumor classification systems that are based increasingly on molecular genetics and that sometimes divide diagnostic entities into smaller and smaller groups in what is already a relatively rare disease. Collaborative pooling of data, cases, and specimens on an international level with well-organized, prospective ascertainment has the potential to uncover clues and exposures in the etiology of childhood brain tumors.

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Clinical Presentation and Associated Syndromes of Brain Tumor

3

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In this chapter we will illustrate the range of clinical presentations of different tumor types and anatomical presentations across the first 25 years of life to offer examples that can be used for teaching and training of healthcare workers and the public. The current gold-standard diagnostic test is a brain scan, using a magnetic resonance imaging (MRI) scan or contrast-enhanced computed tomography (CT) scan. We will go on to consider the research evidence for the range of symptomatology and patterns of referral leading to diagnosis in different health systems, where they have been studied. We will present evidence of a new population-based symptom awareness program called HeadSmart Early Diagnosis of Brain Tumor (www.headsmart.org.uk), directed at informing the public and profession and selecting patients for urgent imaging to diagnose or exclude brain tumor. In this, we will consider the technical challenge of an awareness campaign, how it could be designed, monitored, and modified to tackle referral practice in a national health system using the guidance from an evidence-based clinical guideline seeking to accelerate brain tumor diagnosis. We will identify initiatives that are in development following the example of the HeadSmart campaign. We will conclude by considering how the priority of accelerating diagnosis could lead to a new era of brain tumor diagnosis, treatment, and outcome with reduced risk of brain injury for survivors.

3.1 WHY DO BRAIN TUMORS DEVELOP IN EARLY LIFE?

Nearly all parents ask why their child developed a brain tumor. It is now clear that brain tumors arising during infancy, childhood, adolescence, and early adulthood are strongly influenced by mechanisms of brain growth and development associated with these stages and are therefore, to a large extent, a consequence of disordered brain development. About 10% are associated with known cancer predisposition states and, as detailed genetic sequencing of childhood cases proceeds, more can be expected to be included in this category.[1] It is suggested that mutations in genes and epigenetic abnormalities governing normal brain growth processes favor tissue growth deregulation, leading to tumor formation with particular biological characteristics. This implies that, although there may be environmental factors that contribute to tumor development, the key susceptibility resides in the innate control of brain growth and development processes at a molecular level across the brain's complex anatomical structures. The recent explosion in molecular knowledge has identified complex relationships between tumor type, anatomical location, and age. This new information could be harnessed to develop alternative approaches to diagnosis if biosampling proved to be predictive of either brain injury or specific to tumor types which are known to develop at key points in development. The experience of monitoring for optic pathway glioma in neurofibromatosis type 1 (NF1), acoustic neuroma and spinal ependymomas in neurofibromatosis type 2, and subependymal giant cell astrocytomas (SEGAs) in tuberous sclerosis are illustrative of the potential for clinical benefit from prospective surveillance or screening.[2–4] The alternative and current symptomatic approach to case ascertainment risks the irreversible brain injury associated with symptomatic presentation in such conditions, affecting vision, hearing, hormonal functioning, paralysis, and acute hydrocephalus, with its consequences for cognitive capacity. Detecting this brain injury as early as possible self-evidently offers benefits for the developing child and their family. The challenge is to predict it with a level of sensitivity and specificity compatible with acceptable practice for the children and families involved.

3.2 WHAT ARE THE RISKS OF GETTING CANCER AND BRAIN TUMORS IN EARLY LIFE (<25 YEARS)?

The cumulative risk for a young person developing cancer of any type from birth to 25 years of age is 1/450 by age 15 and 1/300 over the 10 years of age from 15 to 24, adding up to a cumulative risk of 1/180 from birth until age 25.[5] This is undoubtedly a significant health risk for young people to consider and contradicts the predominant attitude expressed in medical writing that "cancer is rare in childhood."

In contrast it could be said that: "Cancer in childhood is not rare; it is predictable and a consequence of growth and development of specific tissues and is, therefore, unavoidable. Indeed, it is fortunate it does not happen more frequently."

For brain tissue, the cumulative risk for developing a brain tumor are 1/1,700 by age 15 and 1/2,350 over the 10 years of age from 15 to 24, adding up to a cumulative risk of 1/980 from birth until age 25. Brain tumors account therefore for 20–25% of all cancers in the first 25 years of life.[6] Statistics presented in this way, from the individual's perspective, are frequently a shock to practitioners and the public alike and can adjust consideration given to prioritization of brain tumor risk from a diagnostic perspective.

3.3 WHAT IS THE PROGNOSIS FOR BRAIN TUMORS CURRENTLY?

Survival rates have improved over the past three decades from less than 50% to about 70% 5-year survival in first-world countries.[7] These statistics do not apply in developing countries where access to neurosurgery and childhood cancer care can be highly variable. However, in first-world countries brain tumors are now the biggest cancer killer in this very young age group and up to 40 years of age. Such survival statistics have been used to drive practice change in all cancer therapies. For brain tumor, the disability aspects of survivorship are equally important. Limited evidence exists to assess the proportion of survivors with significant disability. Where it has been studied in population cohorts, it would seem that about two-thirds of survivors experience lifelong moderate or severe disability.[8,9] Neurological disabilities affect cognitive capacity, influencing memory, brain processing speed, personality development, and capacity for initiative and therefore impairment of educational achievement. Motor and sensory disabilities affect hearing, vision, and motor function, limiting social functioning and mobility. Endocrine deficiencies, which are lifelong, compromise growth, development, and fertility and the capacity to cope with stress and maintain metabolic rate to control weight gain. Together these disabilities can profoundly affect capacity for socialization and relationship development, remunerative work, and independent living, leaving survivors vulnerable to sudden collapse and death as well as obesity and the associated risks. They create a childhood survivor of great concern for their families and dependent upon disability and chronic health support systems with all the economic consequences for society.

3.4 HOW DOES DIAGNOSTIC DELAY DAMAGE THE BRAIN?

These survivorship deficiencies are secondary to a number of factors which start with the prediagnostic incremental brain damage that occurs due to uncontrolled intracranial hypertension and progressive focal brain injury due to tumor growth and invasion / compression of brain structures. After diagnosis, injury remains an ongoing risk related to the selection and delivery of surgical, radiotherapeutic, and medical interventions / treatments, contributing to the cumulative brain injury for the survivor. For the purposes of this chapter we are going to concentrate upon arguably the most important of these, the prediagnostic brain injury, as it is relevant to every newly diagnosed person at any age. Brain injury present at diagnosis seldom fully resolves, despite theories of plasticity in the developing brain. Where white-matter damage has developed due to raised intracranial pressure, the impact is global upon subsequent brain functioning and may represent a trigger, together with radiotherapy, to enhance the risk of stroke and early-onset dementia during early adulthood. For these reasons strategies for reducing these risks are a top priority for healthcare systems focused upon the needs of the patient and society at large.

3.5 DO ALL HEALTH SYSTEMS TAKE A LONG TIME TO MAKE A DIAGNOSIS?

The neuro-oncology multidisciplinary team plays a very limited, if any, role in the selection of patients for diagnostic scanning to make the initial diagnosis; this is the responsibility of clinicians working in community-based care and general hospitals with access to imaging facilities. There is now a significant literature describing the steps for making a cancer diagnosis as this is now increasingly seen as a strategy to improve outcomes (Figure 3.1).

A wide range of total diagnostic intervals (TDIs) are reported which are skewed towards prolonged delays, with median TDIs ranging from 6 to over 14 weeks and ranges from 1 week to more than a year[11–20] (Figure 3.2). For the family experiencing very prolonged diagnostic intervals, when symptoms have been reported repeatedly to healthcare workers and not acknowledged as indicating the need for a brain scan, this experience reflects badly on healthcare systems and sometimes individual practitioners and can precipitate litigation. To attempt to understand this, it is necessary to consider the range of tumor types that can occur in the brain of humans from birth to early adulthood. Given that they are occurring in the organ that is not only growing and developing itself but also driving the growth and development of the rest of the body, not to mention being the center for cognitive, psychological, and social development of the individual (Figure 3.3) as well as physiological regulation of the being's existence, the symptoms of a tumor growing in this mechanism are bound to be complicated!

3.6 BRAIN TUMOR SYMPTOMS BY ANATOMY AND TYPE

Table 3.1 identifies the common tumor types grouped by their anatomical location, their staging and survival outcomes, as well as the genetic predispositions with which they are associated. We have summarized the common clinical presentations and the nature of brain injuries that survivors may experience. This is an attempt to illustrate that, in childhood, the collective term "brain tumor" is an inadequate term, as it fails to convey the very wide range of entities that are included in the grouping. The challenge for the pediatric practitioner considering brain tumors as a differential diagnosis of a child or adolescent with a new group of symptoms is that there are so many entities to be considered. Their growth within the brain at different stages of childhood with its global impact on the body's functioning means that selecting simple clinical "red flag" symptomatology, i.e., headaches and vomiting, favored in adult cancer diagnostics, has proved impossible to apply to population datasets.[23] To make progress it has proved necessary to break the problem down anatomically and by stages of development. Furthermore, in seeking to justify strategies to accelerate diagnosis there is a clinical need to consider what are the potential benefits, tumor type by tumor type, of an earlier diagnosis. For this reason Table 3.1 includes not only patient and tumor factors but also multifactorial contributions to patient survival and

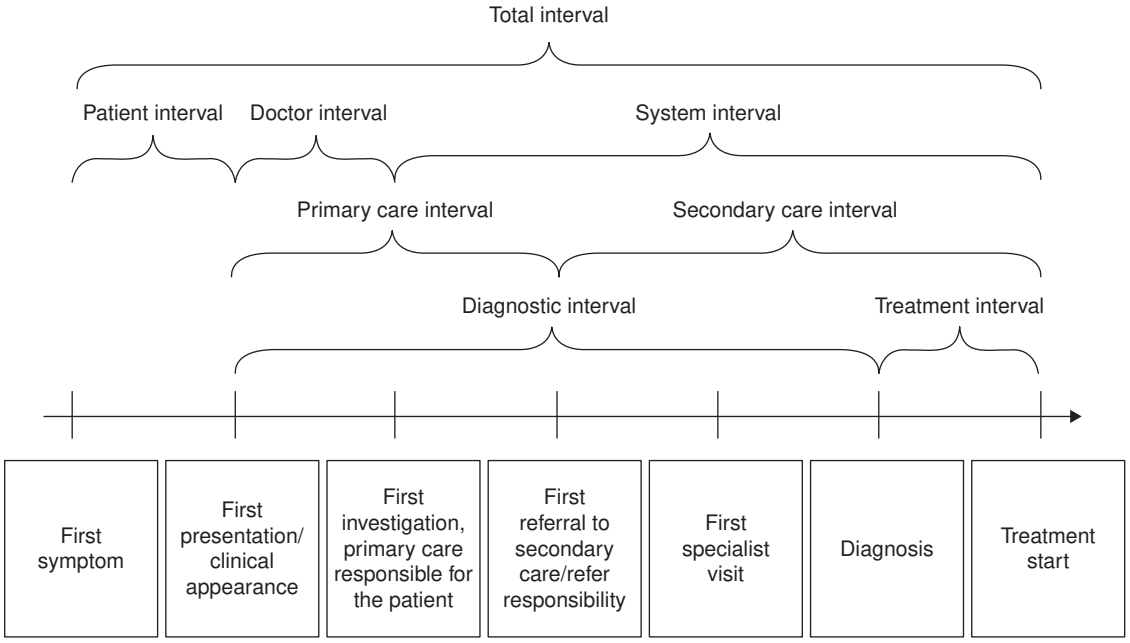


Figure 3.1 The overall milestones and time intervals in the route from first symptom until start of treatment. (Reproduced from Weller et al. [2012],[10] with permission.)

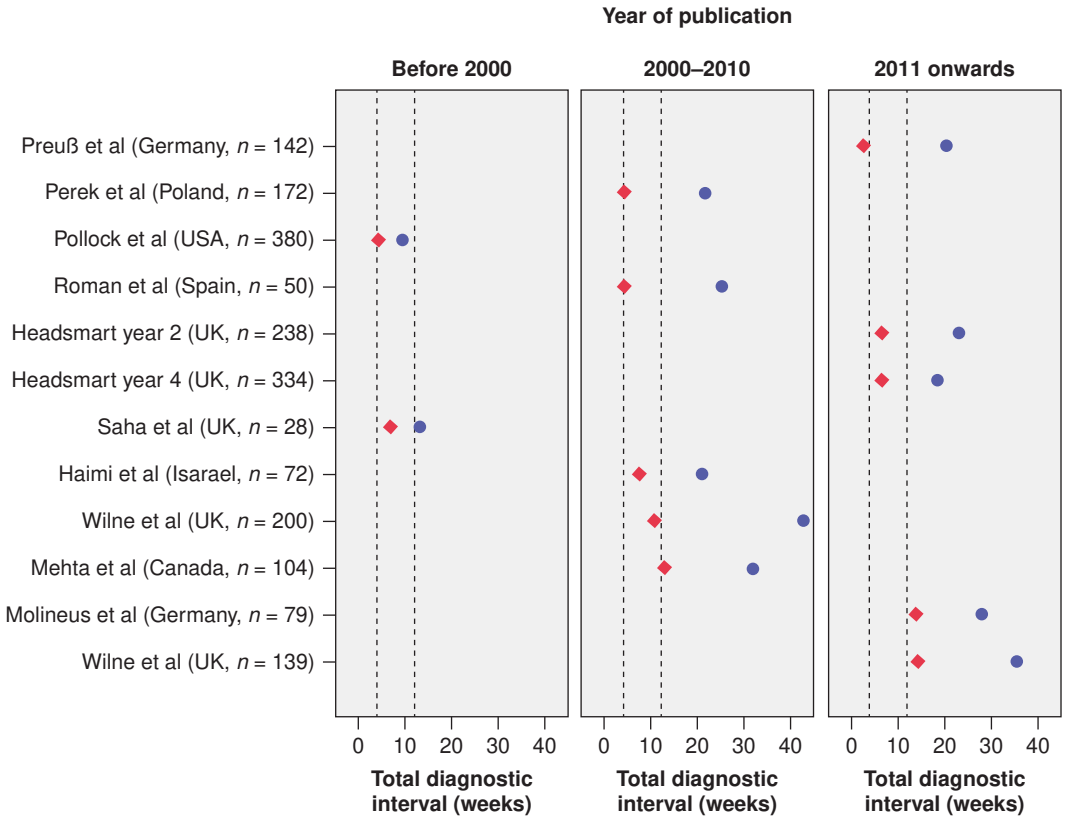


Figure 3.2 International comparison of total diagnostic interval.

disability outcomes. Efforts in healthcare aimed at accelerating diagnosis would be justified if they resulted in saving lives from sudden death, downstaging to better prognostic groups, or reducing consequent disabilities for those who are cured. It could be hypothesized that, as brain tumors in childhood are a product of brain development affecting

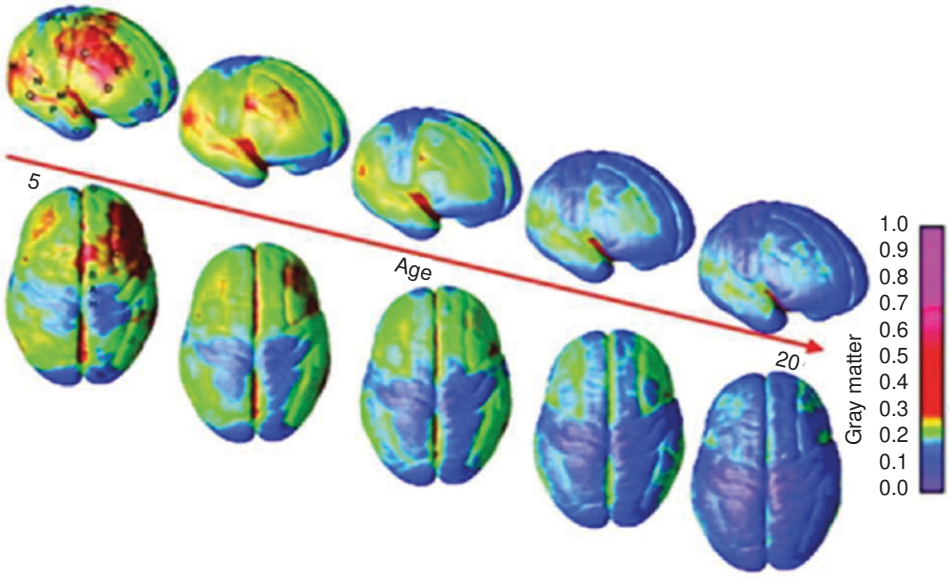


Figure 3.3 Right lateral and top views of the dynamic sequence of gray-matter maturation over the cortical surface. The side bar shows a color representation in units of gray-matter volume. (Reproduced from Gogtay et al. [2004],[22] with permission from the National Academy of Sciences, USA.)

1 in 1,000 by age 25, a screening / surveillance strategy might be justified if a sensitive and specific test was available to predict or detect tumors in their presymptomatic stage. The initiative's justification would be underlined by comparison with population genetic screening for inborn errors of metabolism, which are 10-fold less common, or cystic fibrosis with a comparable incidence to brain tumor by age 15 years. As such a test does not yet exist, we will have to consider in detail symptomatic presentation of brain tumors and the consequences for the young patients who experience them.

3.7 SYMPTOMS OF RAISED INTRACRANIAL PRESSURE

Brain tumors present clinically in less than 50% of cases with signs of raised intracranial pressure that can fluctuate in severity over time. The source of this raised pressure due to brain tumor is a product of:

- Expanding tumor mass
- Obstructive hydrocephalus
- The increasing rigidity of the skull over the first 2 years of life.

Once the skull bones have fused, the brain can still compensate for raised pressure by adapting blood flow. However, when this compensation has been exhausted rising cerebral perfusion pressure results in an accelerated rise in intracranial pressure impairing tissue oxygenation and causing brain damage (Figure 3.4). If unrelieved it leads to herniation of brain contents from the middle to posterior fossa and through the foramen magnum, causing death.

Sustained subacute decompensation of this type primarily affects white-matter or fiber tracts, which can be seen as papilledema or swelling of the optic discs in the eye. If unrelieved over hours, the nerves are irreversibly damaged, leading to blindness. The same process can occur throughout the white-matter tracts; its acute changes are identified as cerebrospinal fluid extravasation to white matter on MR scanning as well as structural changes linked to hydrocephalus and brain swelling. Consequently leukoencephalopathic changes due to white-matter atrophy can develop and be associated with global impaired function (Figure 3.5).

3.8 WHAT CAN WE LEARN FROM THE LITERATURE ABOUT SYMPTOMATOLOGY?

The publication by Wilne et al. in 2007[25] used a systematic literature review to identify the evidence for ranking the frequency of symptoms for tumors arising in different parts of the brain and different ages of patient. It also considered the impact of the coexistence of NF1 as a common genetic condition recognized as a trigger for optic pathway gliomas in particular. This systematic review was repeated in 2016 and was further used to refine the anatomically determined triads of commonest symptoms stratified by age and anatomical region.[26] Although the symptomatology remained unchanged, the number of papers published across the two time periods had more than doubled, highlighting a greater interest and understanding of the importance of the symptom profile in brain tumor presentation (Figure 3.6).

3.9 SUBGROUP ANALYSES

These reviews have permitted comparison of ranked symptom intervals of all brain tumor types, by age, NF1 status, and three commonest anatomical groups: brainstem, central, and cerebellar (Figure 3.7). They highlight that

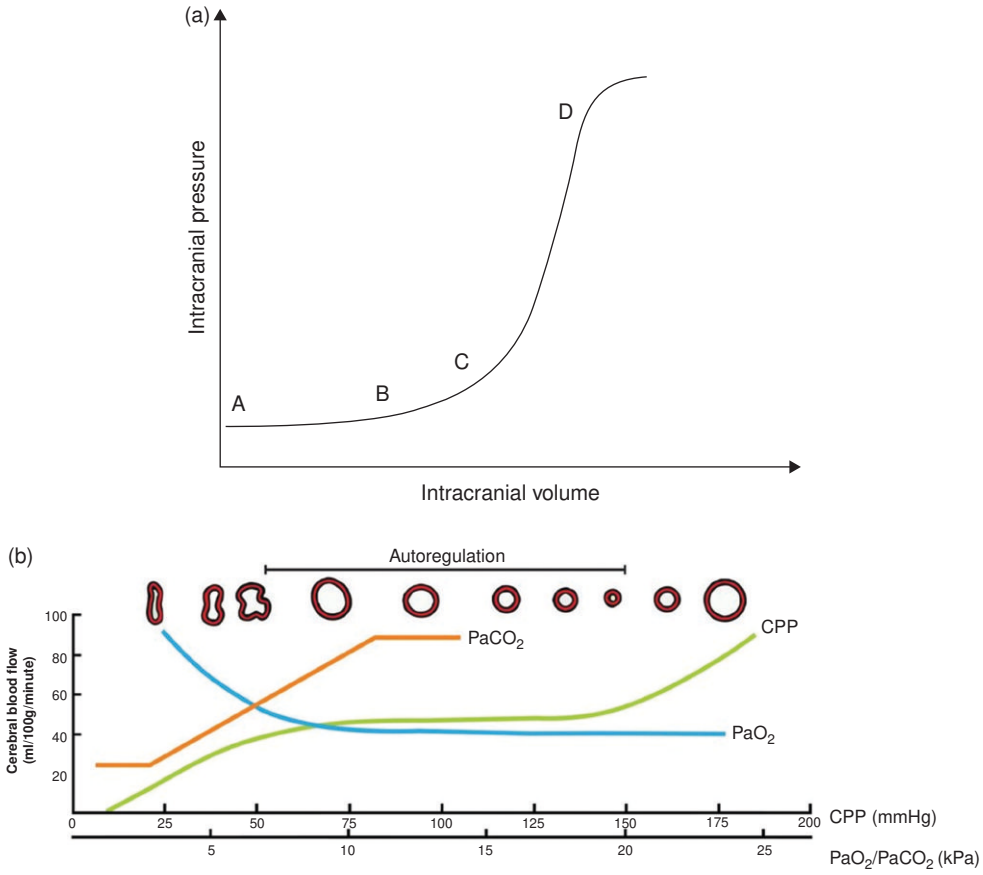


Figure 3.4 (a) Modulation of intracranial pressure with rising cerebral volume; (b) pathophysiological mechanisms of raised intracranial pressure. CPP, cerebral perfusion pressure; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen. (Reproduced from Tameem and Krovvidi [2013],[24] with permission.)

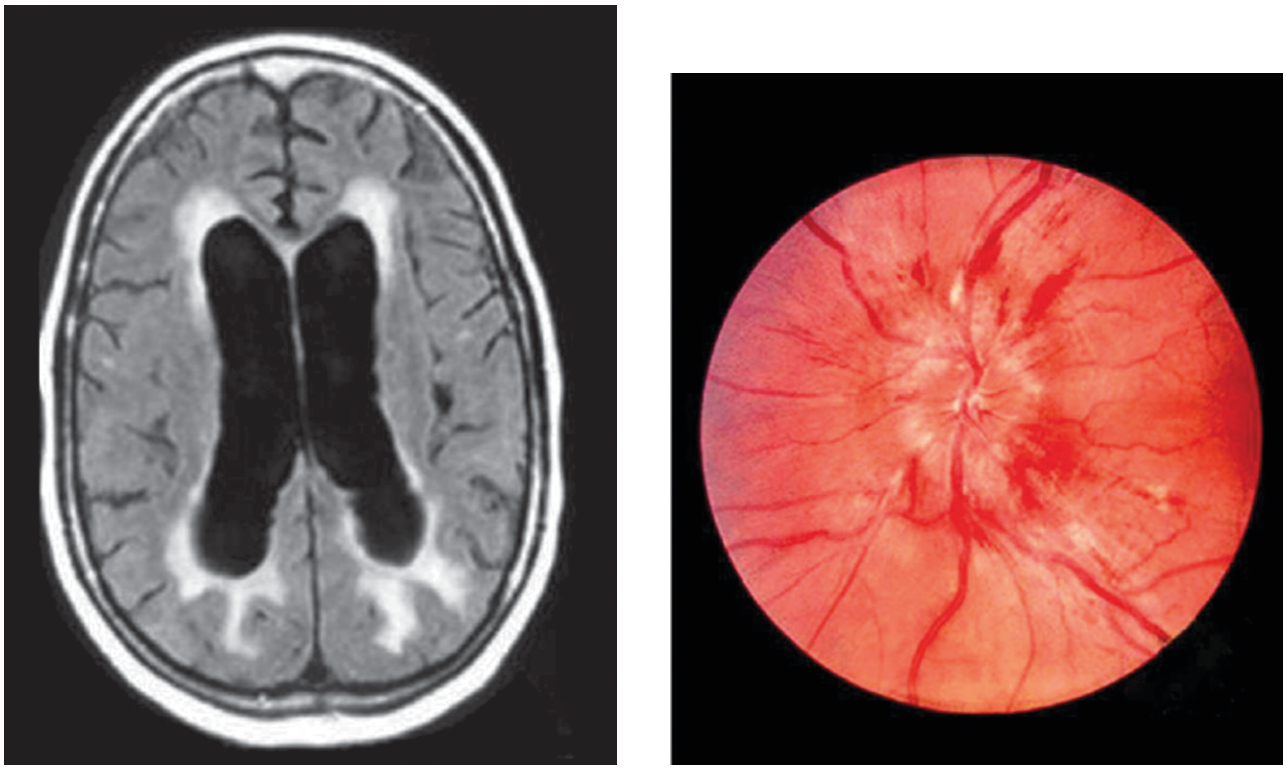


Figure 3.5 Cerebrospinal fluid extravasation associated with (a) hydrocephalus and (b) papilledema of optic disc.

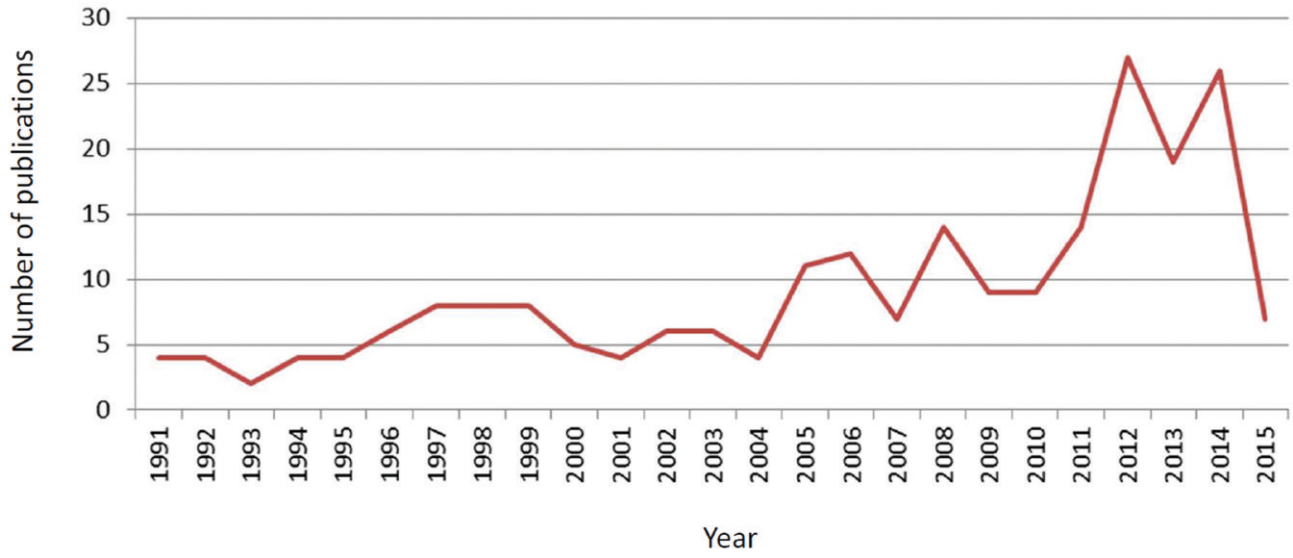


Figure 3.6 Publication trend over both systematic reviews.

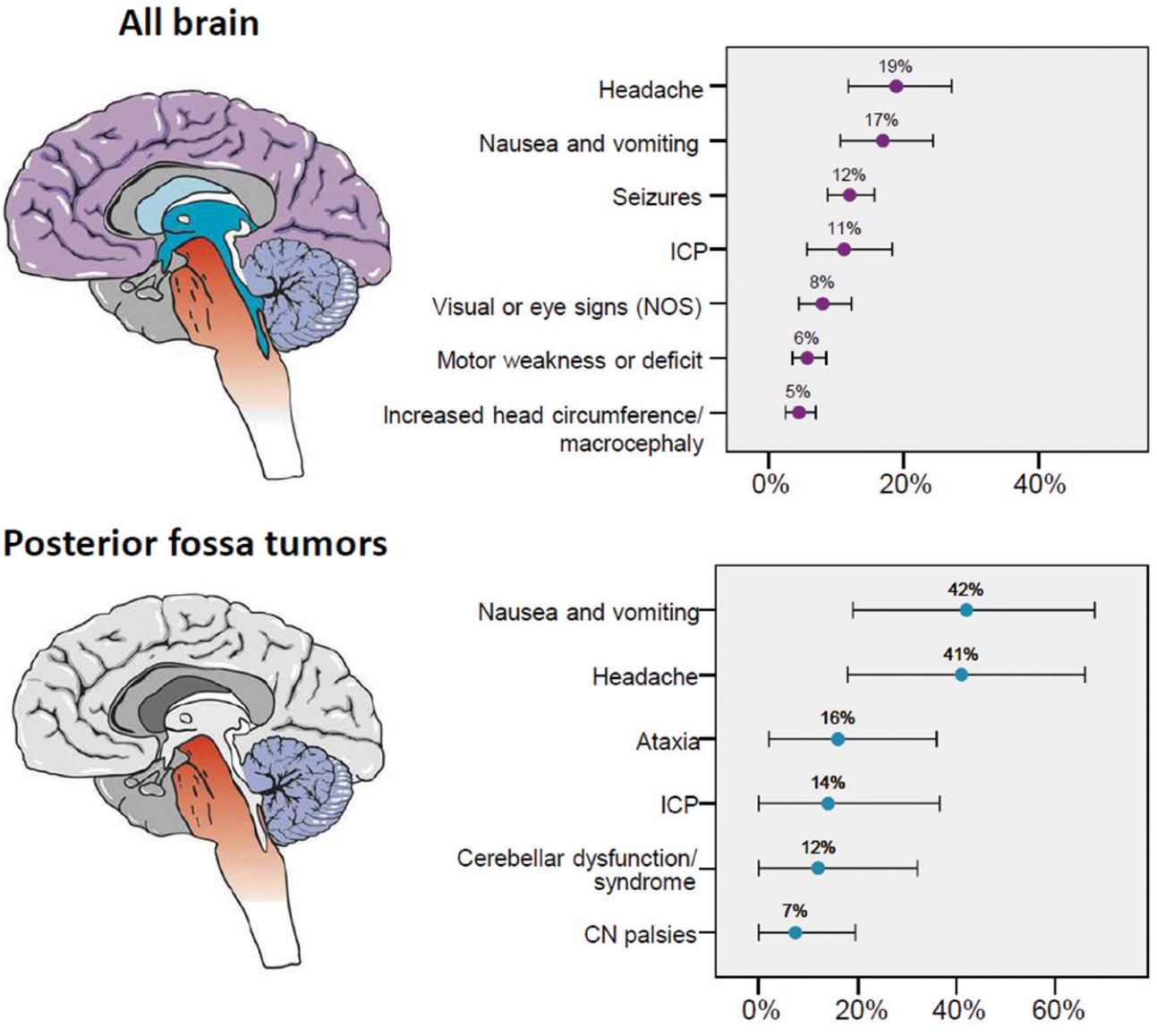


Figure 3.7 Systematic review identifying ranked symptoms by anatomical location of tumor: (a) all brain; (b) posterior fossa tumors; (c) central tumors; (d) brainstem tumors. CN, cranial nerve; ICP, intracranial pressure; NOS, not otherwise specified. (Data from HeadSmart [2017].[29])

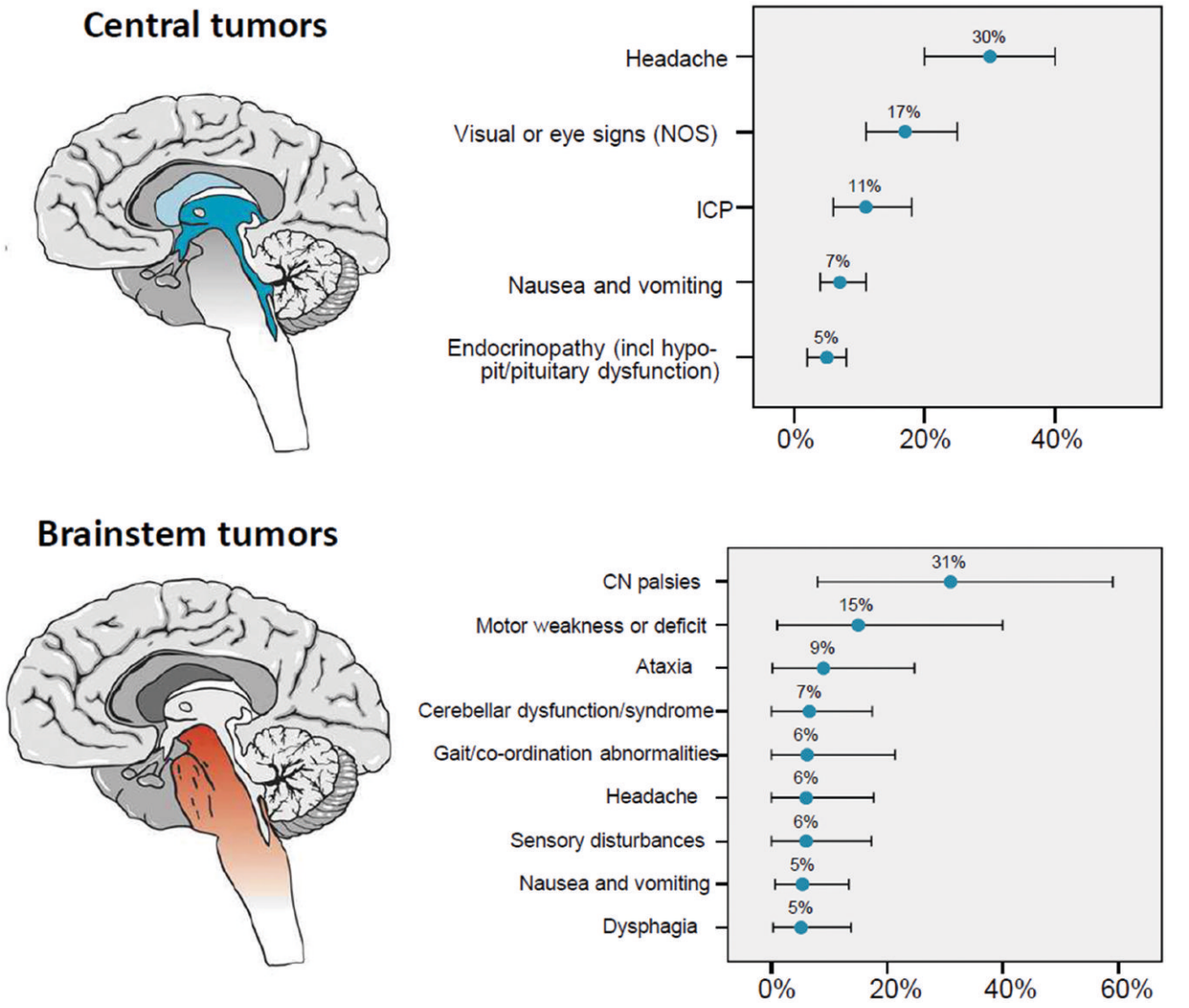


Figure 3.7 (cont.) Systematic review identifying ranked symptoms by anatomical location of tumor: (a) all brain; (b) posterior fossa tumors; (c) central tumors; (d) brainstem tumors. CN, cranial nerve; ICP, intracranial pressure; NOS, not otherwise specifi ed. (Data from HeadSmart [2017].[29])

headache and vomiting, whilst a common presenting sign / symptom in cerebellar tumors, can be combined with signs of cerebellar dysfunction in the classic childhood triad. This affects only about 30% of cases. Headache without vomiting is common in central tumors linked to endocrine problems and visual signs. Although brainstem tumors present with focal neurological signs affecting facial movement, squint, swallowing, and gait, headache is infrequent.

There are interactions between tumor type and TDI data, with the lower-grade tumors being associated with longer TDIs compared to higher-grade tumors. This is particularly marked in central tumors where the infrequency or late development of raised intracranial pressure and slow onset of endocrine symptoms or visual field loss can frequently develop insidiously before being noted by patients, family, or practitioner.

3.10 NF1-LINKED TUMORS

Figure 3.8 identifies the ranked symptomatology for patients with and without NF1, highlighting the predominance of visual symptomatology in NF1 children. This feature, combined with the early age of development of optic pathway glioma, justifies the existing visual screening recommended for children with NF1, although using the detection of measurable vision loss as a screening test to prevent / limit vision loss does not seem to meet criteria for a successful screening program. There is controversy surrounding the use of brain scanning in this patient group as multiple abnormalities may be detected on scans which may not represent a threat to vision or predict tumor formation and so can be distracting and a source of great parental concern. Children with NF1 can also develop tumors in other areas of the brain, both grade I pilocytic tumors of the cerebellum and high-grade gliomas of cortical regions.

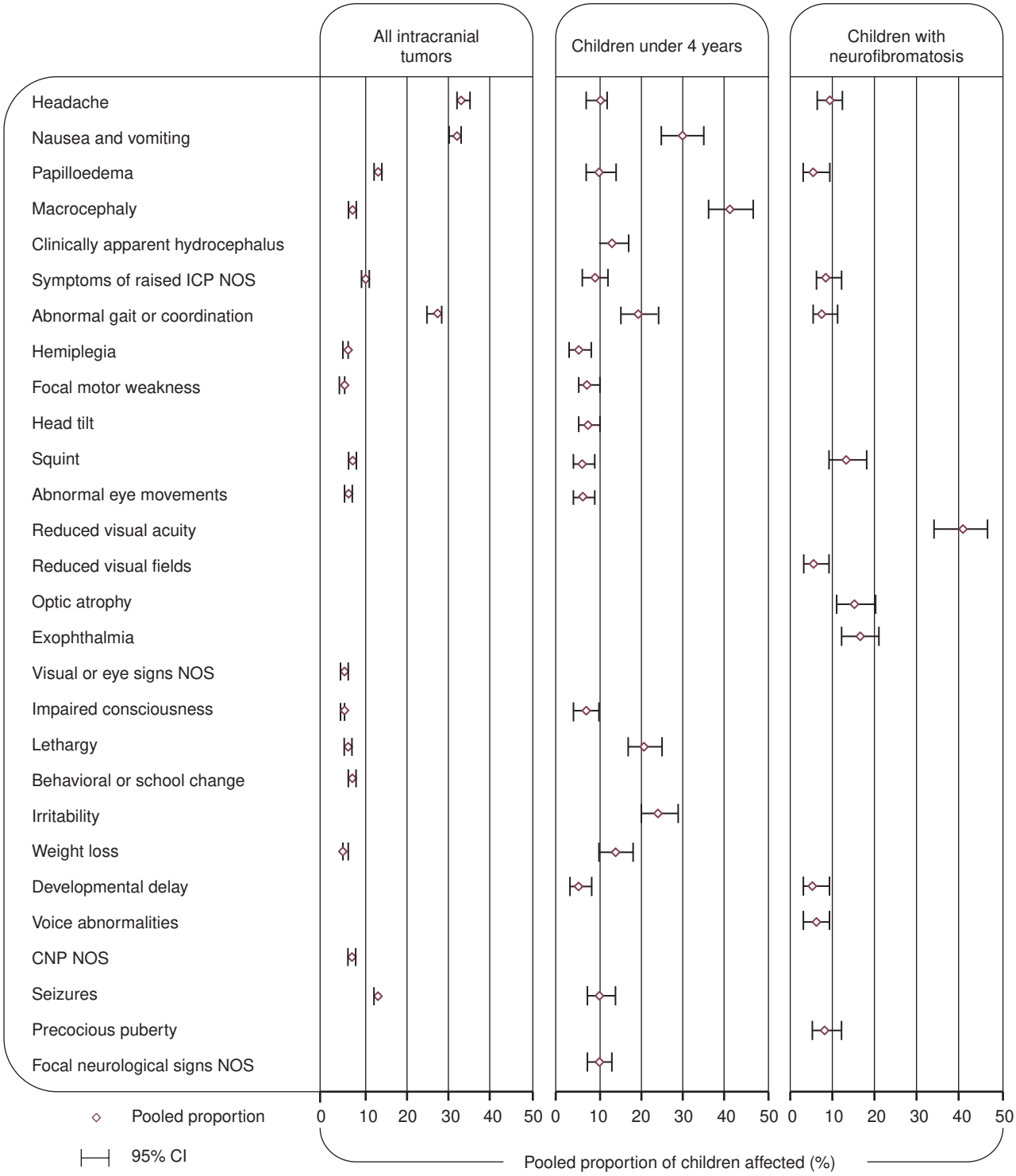


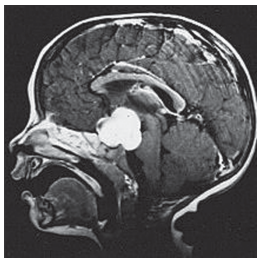
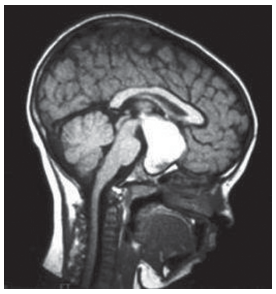
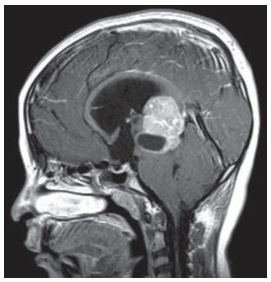
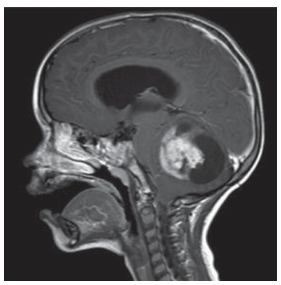
Figure 3.8 Frequency of symptoms and signs in children with intracranial tumors. CI, confidence interval; CNP, cranial nerve palsy; ICP, intracranial pressure; NOS, not otherwise specified. (Reproduced from Wilne et al. [2007],[25] with permission.)

The lack of reliable data on the natural history of such lesions on scanning means that it is hard to predict outcome in individual cases without close observation. The new group of mitogen activated protein (MAP) kinase inhibitor drugs potentially targeting the *BRAF* mutations have been reported as particularly effective in plexiform neurofibroma and consequently they have been prioritized for trial in NF1 optic pathway glioma to treat those with progressive visual loss. This therapeutic enthusiasm highlights the risks of treating patients where the natural history is uncertain.

3.11 WHAT CONTRIBUTES TO DELAYS IN DIAGNOSIS?

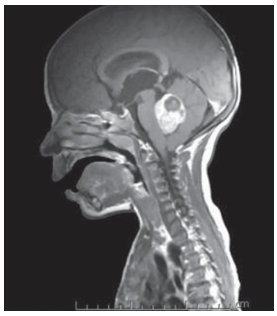
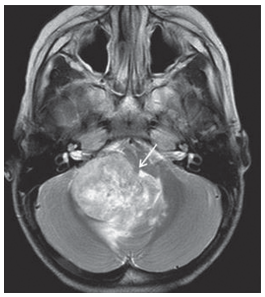
The primary care health team are frequently consulted about children with non-specific symptoms which are

Table 3.1a Anatomical distribution of childhood brain tumor types: midline supratentorial, cerebellar, brainstem, and cortical

Midline supratentorial tumors		Symptomatology
	***Hypothalamic astrocytoma: classically grade 1 pilocytic*** Age: <5 years Genetic association: family brain tumor syndrome, occasionally NF1 Staging: hazard ratio (HR): age <2 years; 5–10% metastatic to leptomeninges Survival: standard risk (SR) 90% 10-year survival HR 50–60% 5-year survival Survivorship: blindness, hypopituitarism, global brain damage 2° to hydrocephalus and tumor mass	**Under 2 years of age** Presentation in the first 2 years of life is with persistent vomiting, poor weight gain but normal height / length, accelerating head growth, and abnormal eye movements. They should be considered in investigation of more severe cases of poor weight gain where persistent vomiting is the cause. The child is typically cheerful, emaciated, and hyperactive, as described in diencephalic syndrome. Abnormal eye movements such as eye bobbing or vertical nystagmoid movement and squint are often characteristic. Endocrine investigations show hypothalamic suppression **Later in childhood** When tumors in this location present in later childhood / adolescence, classic features include headaches, growth problems, obesity, precocious or delayed puberty, symptoms of pan-hypopituitarism, including diabetes insipidus, and oculomotor abnormalities, visual field defects, and alterations in mood. The differential diagnosis includes atypical anorexia nervosa in girls or boys, unexplained behavioural change in adolescence, arrested /slow pubertal development
	***Craniopharyngioma*** Age: peak in childhood and middle/ old age Genetic association: none Staging HR: tumor size >28 mm[21] Survival: >85% 10-year survival Survivorship: blindness, hypopituitarism, hypothalamic syndrome, consequences of focal radiotherapy	
	***Intracranial germ cell tumor*** Age at presentation: during puberty; M>F Genetic association: Down syndrome, Asian origin Staging: SR non-secreting (germinomatous) tumors M– HR secreting (non-germinomatous) tumors, M+ Survivorship: blindness, hypopituitarism, global brain damage 2° to hydrocephalus, consequences of focal or craniospinal radiotherapy	**Intracranial germ cell tumors** classically present with headaches and vomiting due to raised intracranial pressure which can contribute to poor weight gain, endocrine abnormalities, including diabetes insipidus, and the onset of oculomotor abnormalities classically described as Parinaud's syndrome or dorsal midbrain syndrome, vertical gaze palsy, and sunset sign. These signs describe an inability to move the eyes up and down. It is caused by compression of the vertical gaze center at the rostral interstitial nucleus of the medial longitudinal fasciculus. It can be seen from this image that the midline tumor is compressing the upper end of the mid brain
Cerebellar tumor types		**Symptomatology**
	***Cerebellar astrocytoma (pilocytic)*** Age: 3–12 years Genetic association: NF1 Staging: SR complete resection, HR incomplete resection Survival: SR > 90% 10-year HR 70% 10-year Survivorship: posterior fossa syndrome / cerebellar mutism, global brain damage 2° to hydrocephalus	**The clinical presentations** of these three childhood cerebellar tumors are not sufficiently characteristic to differentiate one from another before scanning and tissue / biodiagnosis. They present with the **classic triad of headaches, vomiting, and ataxia**. Papilledema, when present, indicates sustained raised pressure and risk of vision loss. In infants, rapid head growth may be the presenting sign. At all ages they may be associated with a sixth-nerve palsy as a false localizing sign of raised intracranial pressure. Head tilt / torticollis can be a feature as a consequence of a postural adaptation to double vision or dural stretching by tumor or hydrocephalus. The severity of the headaches and vomiting commonly fluctuates, sometimes offering a

(*continued*)

Table 3.1a Anatomical distribution of childhood brain tumor types: midline supratentorial, cerebellar, brainstem, and cortical (cont.)

Cerebellar tumor types		Symptomatology
	***Medulloblastoma*** Age: 2–15 years Genetic association: ataxia telangiectasia Staging: SR M–, favorable molecular subtypes HR: M+ unfavorable molecular subtypes Survival: SR >80% 5-year survival HR ~50% 5-year survival Survivorship: posterior fossa syndrome / cerebellar mutism, hypopituitarism, global brain damage 2° to hydrocephalus	false sense of security. The shorter symptom interval may indicate a rapidly growing malignant tumor type. Sudden onset of severe symptoms or symptoms persisting or progressing within 2 weeks indicates a need for urgent brain scanning. Untreated, these symptoms progress to acute hydrocephalus, collapse, and the risk of sudden death if raised intracranial pressure is not managed. The longer the delays in this acute phase, the greater the risk of irreversible global brain injury **Associated genetic predisposition syndromes** justify looking for: **Café-au-lait patches**, associated with NF1, constitutional mismatch repair syndrome **Rubinstein–Taybi syndrome** (or broad thumb-hallux syndrome): short stature, moderate to severe learning difficulties, distinctive facial features, and broad thumbs and first toes **Mucocutaneous telangiectasia** associated with ataxia telangiectasia **Multiple basal cell carcinoma** of skin characteristic of basal cell nevoid syndrome **Enquire about a family history of:** **Familial adenomatous polyposis** (FAP) syndrome: colonic polyps and brain tumor **Dicer1 syndrome**: an inherited disorder with enhanced risk of benign and malignant tumors of the lungs (childhood pleuropulmonary blastoma), kidneys (childhood cystic nephroma), ovaries, and thyroid (multinodular goiter and thyroid cancer) **Li–Fraumeni syndrome** (early breast cancer and childhood sarcoma *p53* mutation)
	***Cerebellar ependymoma*** Age: 0–5 years Genetic association: NF2 Staging: SR complete resection, M–, favorable molecular subtypes; HR incomplete resection, M+ unfavorable molecular subtypes Survival: SR 60% 5-year OS; HR <30% 5-year OS Survivorship: cerebellar mutism syndrome, cranial nerve palsies after surgery, hypopituitarism, global brain damage 2° to hydrocephalus and extended field radiotherapy	

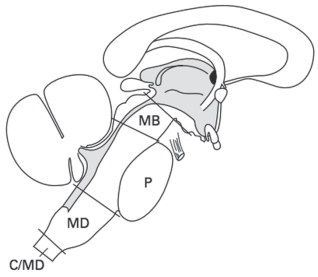
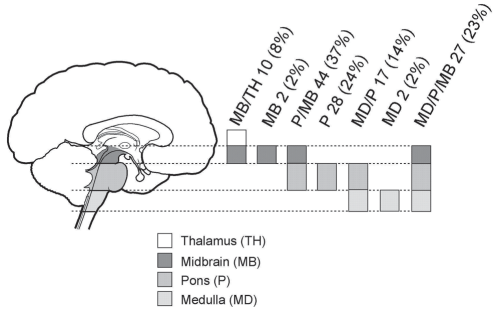
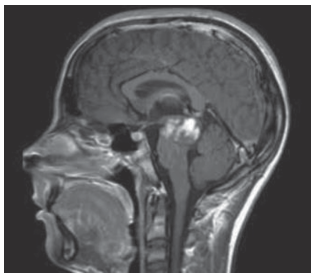
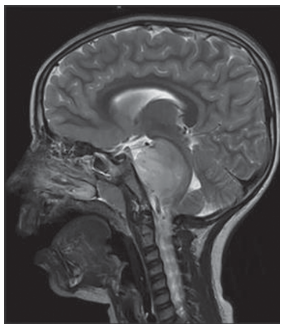
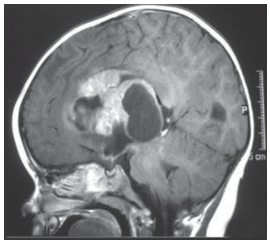
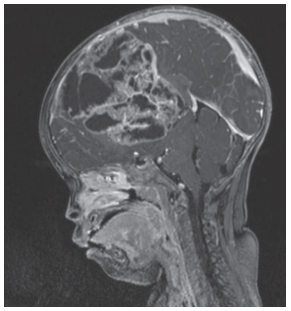
Brainstem tumors		Symptomatology
 	***Diagram of distribution of anatomical brainstem tumors***	Symptoms are linked to the precise anatomical location of the tumor within the brainstem; grouped by midbrain (MB), pons (P), and medulla (MD), and cervicomedullary junction (C/MD). They may extend over these boundaries and involve multiple regions Low-grade tumors present with slowly progressive symptoms whereas rapidly progressive symptoms are indicative of higher grade. Biopsy is now considered necessary for biocharacterization of all brainstem tumors. Where tumors are focal or exophytic in the brainstem or tumors of the cervicomedullary region, then surgical debulking can be considered. Where tumors are intrinsic and diffuse, resection has no therapeutic benefit

Table 3.1a Anatomical distribution of childhood brain tumor types: midline supratentorial, cerebellar, brainstem, and cortical (cont.)

Brainstem tumors		Symptomatology
	***Focal grade 1 or 2 astrocytoma of brainstem applicable to MB, MD, and C/MD*** Age: 2–12 years Genetic association: NF1 Staging: debulking, positive predictor, risk of progression reduces >5 years Survival: determined by severity of focal brain injury Survivorship*:* focal brain injury: high brainstem: oculomotor palsies, hemi- / quadriplegia	**Midbrain symptoms** The commonest is the tectal plate glioma typically presenting with obstructive hydrocephalus and symptoms of raised intracranial pressure. Other tumors can present with disturbances of eye movements due to third- and fourth-nerve palsies as well as oculomotor incoordination due to Parinaud's syndrome and motor paralysis of limbs **Medullary and medullary cervical symptoms** Defects of ninth, 10th, 11th, and 12th nerves and the chemoreceptor trigger zone (CTZ) / vomiting center. Symptoms include abnormal tongue movements affecting speech, swallowing, and control of the airway with choking symptoms. They are not typically associated with symptoms of raised intracranial pressure; however, vomiting can be a symptom due to involvement of the CTZ. In tumors involving the cervical region, neck pain, neck and upper-arm motor dysfunction can combine with medullary symptoms **Pontine symptoms** Defects of the fifth, sixth, seventh, and eighth cranial nerves present clinically with disturbed movements of the jaw, paralytic squint with failed abduction of the eye, Bell's palsy, and sensorineural hearing loss. Pontine tumors are typically diffuse and involve most of the pons. Their signs can therefore be unilateral or bilateral; they frequently extend up to midbrain and down to medulla
	***Diffuse intrinsic pontine glioma (DIPG)*** Age: 3–15 years Genetic association: NF1 Staging: improved prognosis with longer symptom duration, age ≤3 years, and use of chemotherapy + radiotherapy); poorer prognosis tumor rim enhancement on imaging Survival: <10% 2-year survival Survivorship: Rare with DIPG, focal brainstem injury, hemiplegia, quadriplegia, paraplegia, bulbar palsies	
Supratentorial tumors		
	***Atypical teratoid rhabdoid tumor (ATRT)*** Age: <5 years Genetic association: *SMARC1B* mutation Staging: SR M–, molecular sub-type HR: M+, molecular subtype Survival: SR 40–50% HR: <30% Survivorship: Focal brain injury, blindness, developmental delay	These are all fast-growing tumors that can disseminate and present acutely. In those that present in the first 2 years of life they present with bulging fontanel, rapid head growth, developmental delay, collapse due to acute hydrocephalus, as well as rapid onset of focal signs, i.e., hemiparesis, blindness, focal or generalized epilepsy In older children symptoms mimic those of adults with symptoms of headaches and vomiting, 6th nerve palsy, altered mood, weight loss, and focal neurology deficits of focal epilepsy linked to anatomical location
	**Supratentorial primitive neuro-ectodermal tumor (PNET) / ETANTR / high-grade glioma** These are newly defined entities, data are scarce using this classification Age: <5 years Genetic associations: DICER1 Syndrome (specifically medulloepithelioma) - Constitutional Mismatch Repair Deficiency Syndrome (MSH2, MSH6 MLH1, PMS2) - Fanconi Anemia (FANCD1/BRCA2, FANCN, or PALB2) Staging: HR: M+ incomplete resection Survival: data scarce Survivorship: focal neurological injury from tumor compression / invasion of supratentorial structures	

(*continued*)

Table 3.1a Anatomical distribution of childhood brain tumor types: midline supratentorial, cerebellar, brainstem, and cortical (cont.)

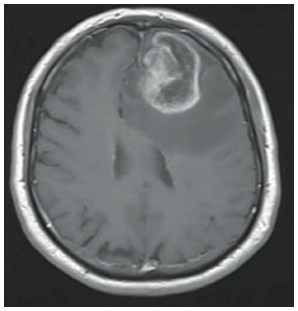
Supratentorial tumors	
	***High-grade astrocytoma / glioblastoma multiforme*** Age: any age Genetic association: Li Fraumeni (TP53) Staging: SR complete resection, M–, favorable molecular features; <3 years at diagnosis HR: incomplete resection, M+, unfavorable molecular features Survival: SR <20% 5-year HR: <20% 5-year Survivorship: determined by anatomical eloquence of tumor location, tumor invasion and surgical and radiotherapy consequences

Table 3.1b Typical brain tumors associated with genetic predisposition syndromes

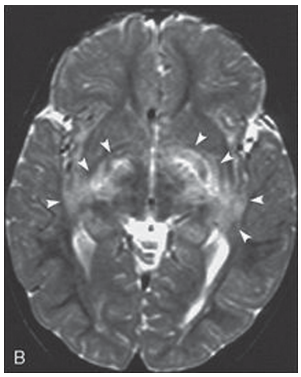
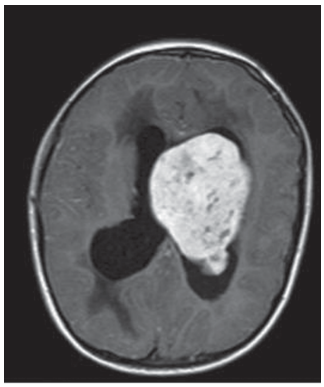
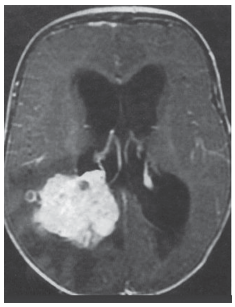
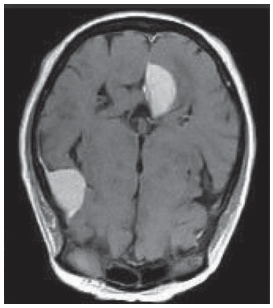
Genetic syndrome-associated tumors		
	**NF1: optic pathway glioma (OPG)** Detected by either vision screening or imaging screening Age: 1–5 years Staging: anatomical staging of optic pathway involvement. Modified Dodge classification Survival: >95% 10-year survival Survivorship: vision preservation dependent on detecting vision change early and initiating treatment. Optic atrophy indicates irreversible optic nerve damage	Skin changes of NF1 with café-au-lait patches are identifiable within the first year; they may be inherited from a parent but new mutations occur OPGs in the first 5 years are commonly detected by visual screening or imaging surveillance. The visual symptoms can be subtle, with strabismus, optic atrophy, and behavior typical of the visually impaired child Differentiating OPG from NF1 imaging changes is sometimes difficult Optic nerve gliomas typically present with proptosis in the first 2 years of life
	***Tuberous sclerosis: subependymal giant cell astrocytoma (SEGA)*** Detected by imaging screening during first 20 years of life Staging: resectable versus unresectable, sensitive to mTOR inhibitors or not Survival: they do not transform; local brain injury threat for hydrocephalus Survivorship: determined by tuberous sclerosis effects on brain function, i.e., epilepsy, consequences of hydrocephalus, learning difficulties, tubers in other organs	SEGAs associated with tuberous sclerosis present in the first 2/3 decades; they are now monitored for with surveillance imaging but can present with acute hydrocephalus when an intraventricular tumor obstructs the interventricular foramen. Treatment with mTOR inhibitors is effective in shrinking tumors and improving epilepsy and appearance of skin manifestations. Surveillance needs to also search for cardiac, renal, and pulmonary manifestations as part of multidisciplinary monitoring

Table 3.1b Typical brain tumors associated with genetic predisposition syndromes (cont.)

Genetic syndrome-associated tumors		
	***Li–Fraumeni syndrome (familial breast cancer p53 mutation)*** ***Infantile choroid plexus tumor*** Age: <5 years Staging: SR: papilloma, M–, complete resection HR: carcinoma, M+/–, incomplete resection Survival: SR: >70% HR: <50% Survivorship: consequences of hydrocephalus, focal brain injury due to surgery and radiotherapy, lifelong secondary cancer risk	These children frequently present as the proband for the Li–Fraumeni syndrome. Choroid plexus tumors present in the first 2/3 years of life with rapid head growth, acute hydrocephalus, and associated signs. The family may be aware of their genetic risk due to earlier screening interventions
	***Multifocal meningioma*** Age >12 years Genetic association: prior cranial radiotherapy, family brain tumor syndromes Staging: SR resectable, HR unresectable Survival: >80% Survivorship: focal neurological injury determined by anatomical site of tumor	These can present clinically with focal neurology related to their anatomical location, focal epilepsy, or as a consequence of surveillance scanning after prior radiotherapy

Abbreviations: ETANTR, embryonal tumors with abundant neuropil and true rosettes; HR, mTOR, mammalian target of rapamycin; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; OS, overall survival; SR, standard risk

self-limiting. The secondary care pediatrician has the challenge of selecting the cases for brain scanning as one of many investigations open to them; in young children, this frequently requires anesthesia for immobilization. The non-neurology specialist has the challenge of selecting cases for brain scanning from children with a wide range of symptoms linked to other organ systems such as gastroenterology, endocrinology, respiratory, psychiatric / psychology, and oto-rhinolaryngology.

3.12 CLASSIFICATION OF INTERVALS BETWEEN SYMPTOM ONSET AND DIAGNOSIS

The international consensus on the system for measuring diagnostic intervals has identified the TDI as the term to include patient and system intervals, highlighting the contribution of multiple intervals to the total. This was proposed as a mechanism for addressing service change discussions. The data on intervals alone do not describe the steps in health services processes that may be contributing to the TDI. The hand-off diagrams offer a visual interpretation for case-by-case analysis (Figure 3.9).[27]

The study of linked population datasets permits referral rates to be analyzed by contact (community versus hospital care) leading up to and after diagnosis, summarizing the intensity of healthcare contacts and permitting the study of clinical variables of the patterns / durations of referral[28,29] (Figure 3.10).

The non-specific nature of initial symptomatology in brain tumor poses a particular diagnostic challenge for families and the clinicians who have to decide whom to refer or select for brain scanning and what priority to put on the scan request. The signs and symptoms that precede diagnosis are initially non-specific, fluctuate in severity, and can mimic other common illnesses. Their progression however can be rapid or gradual, dependent upon the speed of growth of the tumor and its anatomical location. Their diversity means that many specialists may be referred patients with symptoms relevant to their specialty which have their origin in the brain (Figure 3.11).[29]

3.13 RED FLAG SYMPTOMS OR SYMPTOM CLUSTERS

Cancer diagnosis research in adult practice has produced the idea of "red flag" symptoms as those which statistically indicate the need for investigation to diagnose or exclude serious diagnoses for which timely intervention can be important. Respiratory symptoms such as persistent cough for more than 6 weeks, blood in stools or urine, post-coital bleeding, and alterations in pigmentation in moles in the skin have been studied and been shown to have positive predictive value for diagnostic precision. Similar studies in children with brain tumors have not been able to identify "red flag" symptoms with significant positive predictive value.[23] For this reason the Children's Brain Tumour Research Centre undertook a project to perform a

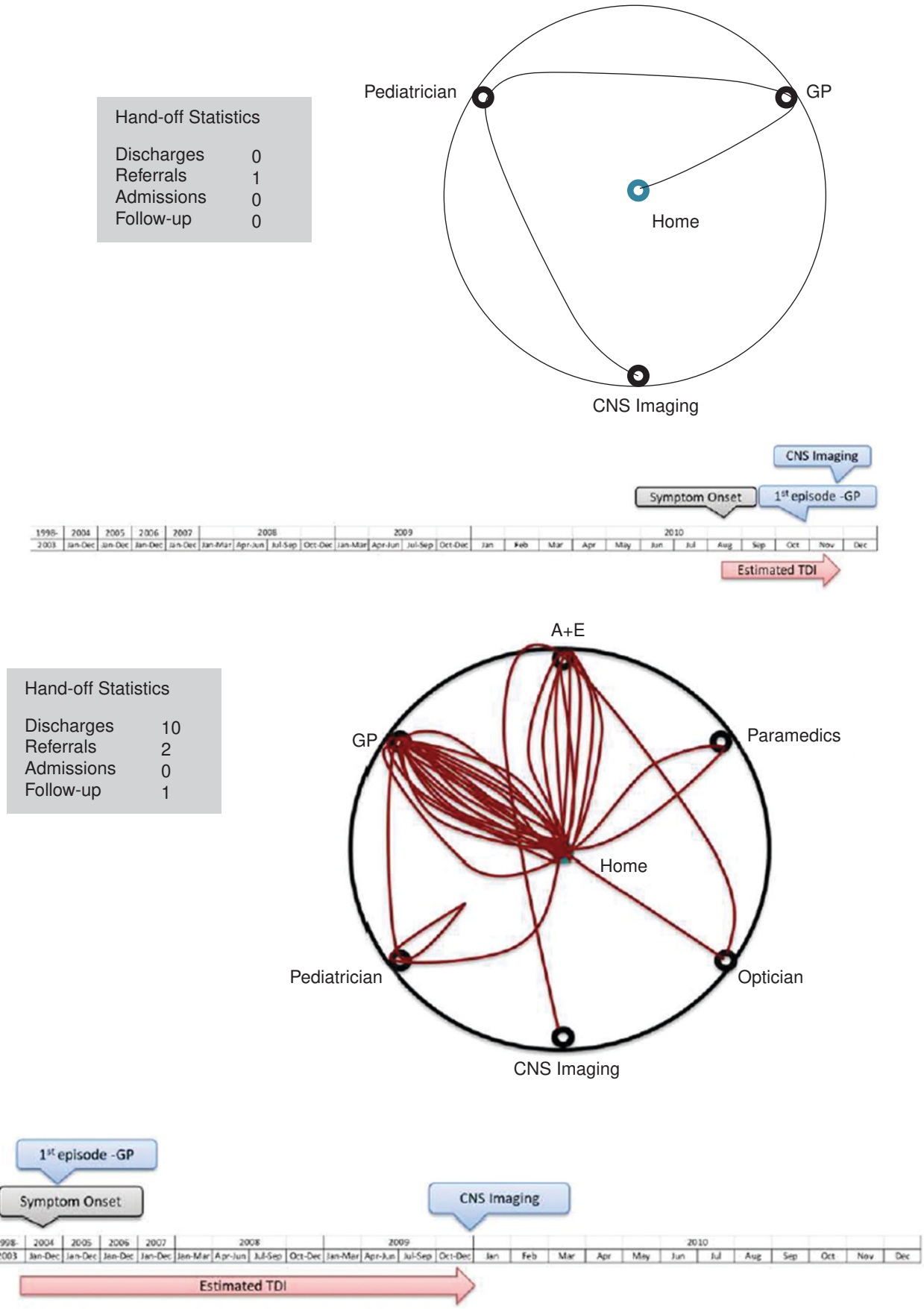


Figure 3.9 (a, b) Hand-off diagrams of two individual patient pathways from symptom onset to diagnosis. A+E, accident and emergency; CNS, central nervous system; GP, general practitioner; TDI, total diagnostic interval. (Reproduced from Walker et al. [2013],[27] with permission.)

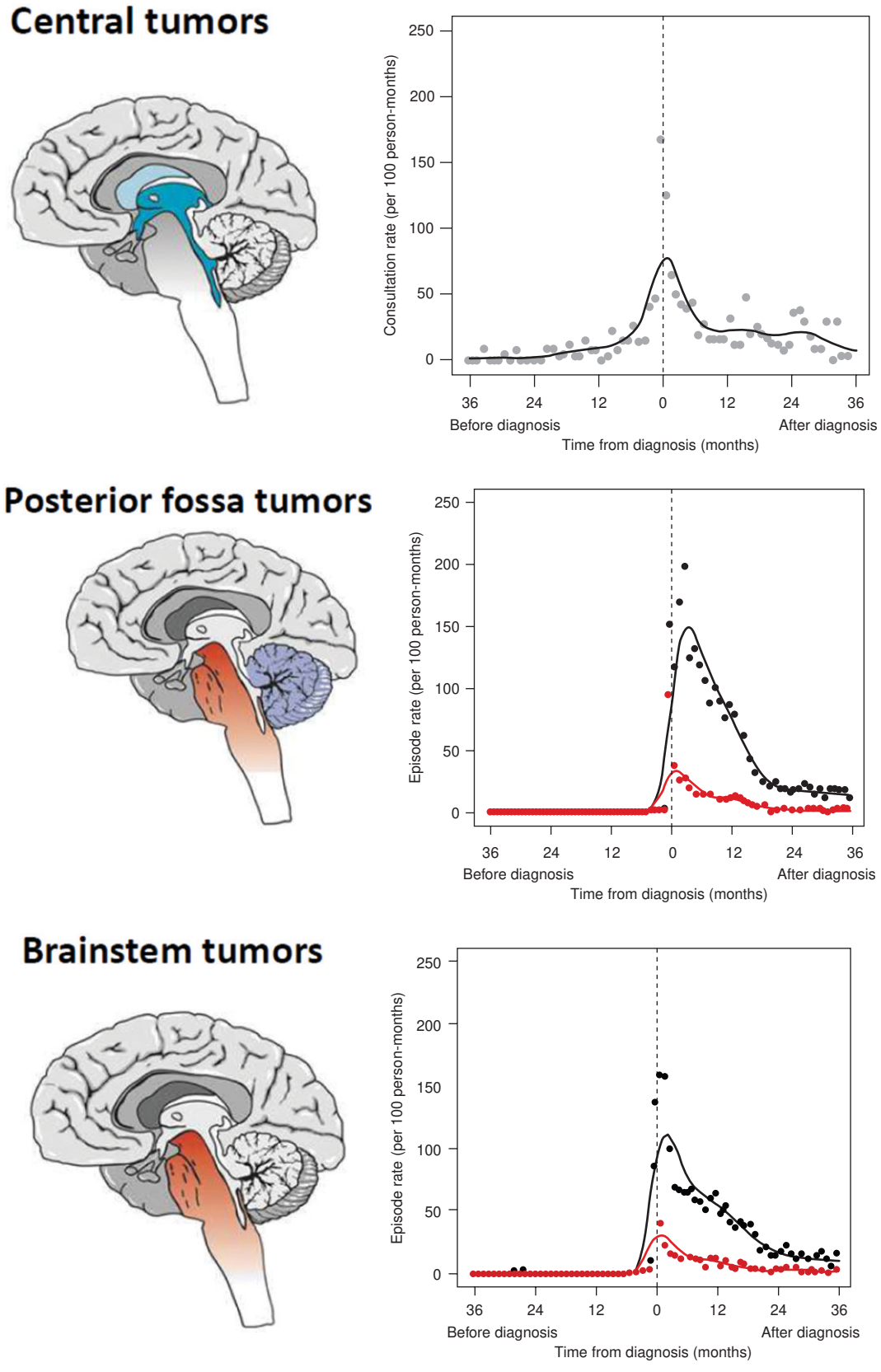


Figure 3.10 Common signs and symptoms of pediatric brain tumors and pattern of hospital presentation: (a) central tumors; (b) posterior fossa tumors; (c) brainstem tumors. Pattern of hospital presentations in children and young adults before and after diagnosis (time = 0): England 1997–2006. Change in monthly rates of all presentations (black dots) after locally estimated scatterplot smoothing (LOESS: black line), and of emergency presentations (red dots) after LOESS smoothing (red lines). (Adapted from Chu et al. [2017],[28] with permission.)

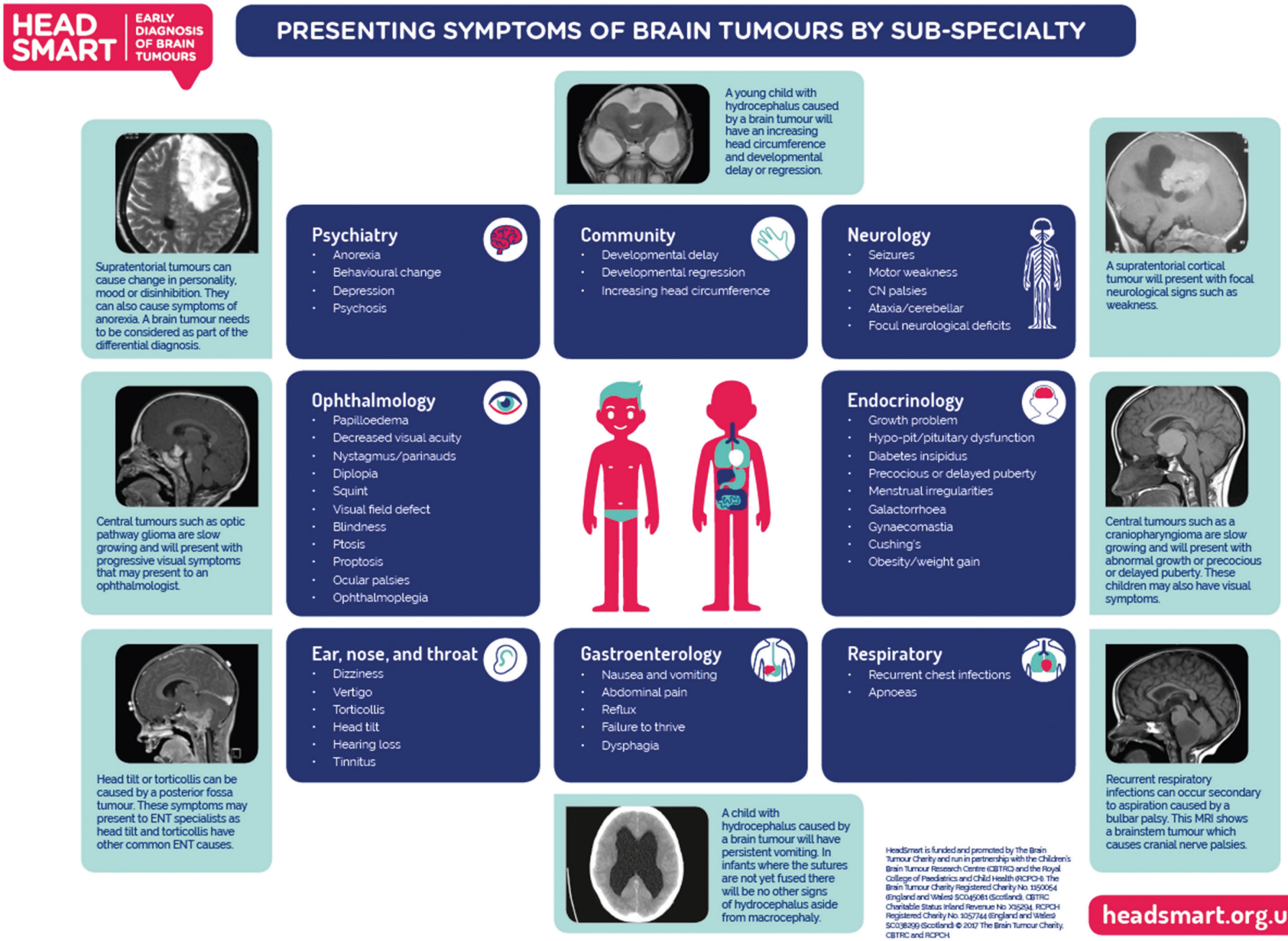


Figure 3.11 Presenting symptoms of brain tumors by subspecialty. (Reproduced from HeadSmart [2017],[29] with permission. Available online: www.headsmart.org.uk/clinical/healthcare-resources/.)

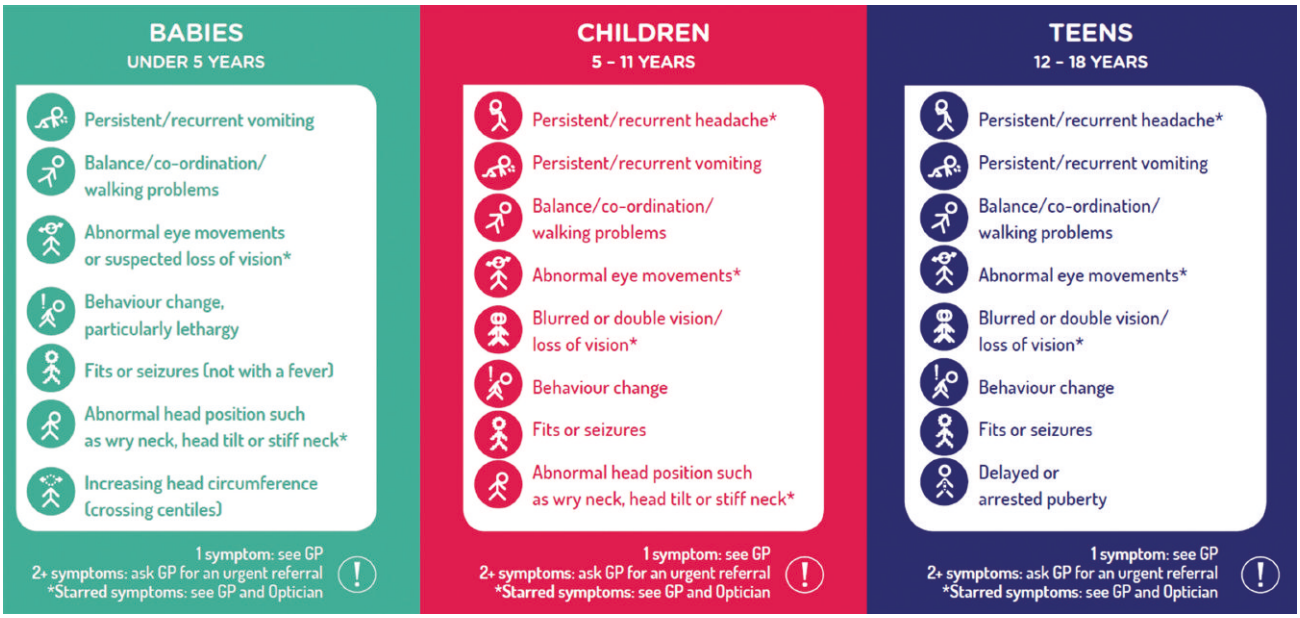


Figure 3.12 HeadSmart symptom card. (Reproduced from Headsmart.org.uk, with permission. Available online: www.headsmart.org.uk/clinical/healthcare-resources/.)

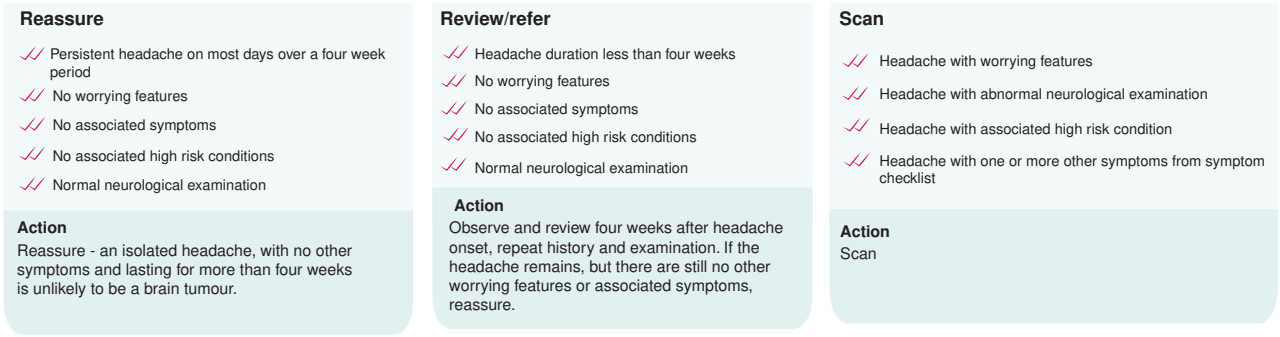


Figure 3.13 Decision support tool for headache. (Reproduced from Headsmart.org.uk, with permission. Available online: www.headsmart.org.uk/clinical/healthcare-resources/.)

systematic literature review and consensus process to write a guideline listing all the symptoms of brain tumor.[29,30]

Whilst undoubtedly comprehensive it was indigestible[31] and further work permitted its representation in an age-stratified symptom list where one symptom justified a clinical consultation and two or more formed a symptom cluster which justified the need for a brain scan (HeadSmart card) (Figure 3.12).

These symptom clusters were described in detail and guidance was offered on when to *refer* for scanning, when and for how long it was reasonable to wait for a *review*, and when it was reasonable to *reassure* (Figure 3.13). This website (www.headsmart.org.uk) was launched in 2011 and accompanied by the identification of children's cancer centers prepared to report TDI data for each new case diagnosed with brain tumor from that time forward. Each center appointed clinical and community champions for their area to deliver the messages of the campaign in person. The project was coordinated by a steering group linking the Royal College of Paediatrics and Child Health, the Children's Cancer and Leukaemia Group, The Brain Tumour Charity, and the Children's Brain Tumour Research Centre at the University of Nottingham which was the data center. This guideline was disseminated to the pediatricians across the UK, personally. Its messages were summarized and disseminated through the media, using marketing techniques, the distribution of millions of symptom cards to children and families, and by creating a national network of centers linking to health system organizations and the local public and educational organizations through the activities of clinical and community champions.

3.14 THE HEADSMART CAMPAIGN QUALITY IMPROVEMENT METHODOLOGY

The summation of intervals that make up the TDI was selected by the HeadSmart campaign as the driver for practice change (Figures 3.14 and 3.15 and Table 3.2).

The figures show how this interval compared across subgroups and over time and also how the components of intervals add to the TDI, describing the steps on the diagnostic journey from first appreciation of symptoms to first medical contact to diagnostic scan date.

These types of data allowed study of clinical and patient factors upon referral steps and can be used to illustrate the challenge for health systems and inform interventions seeking to enhance referral practice and processes.

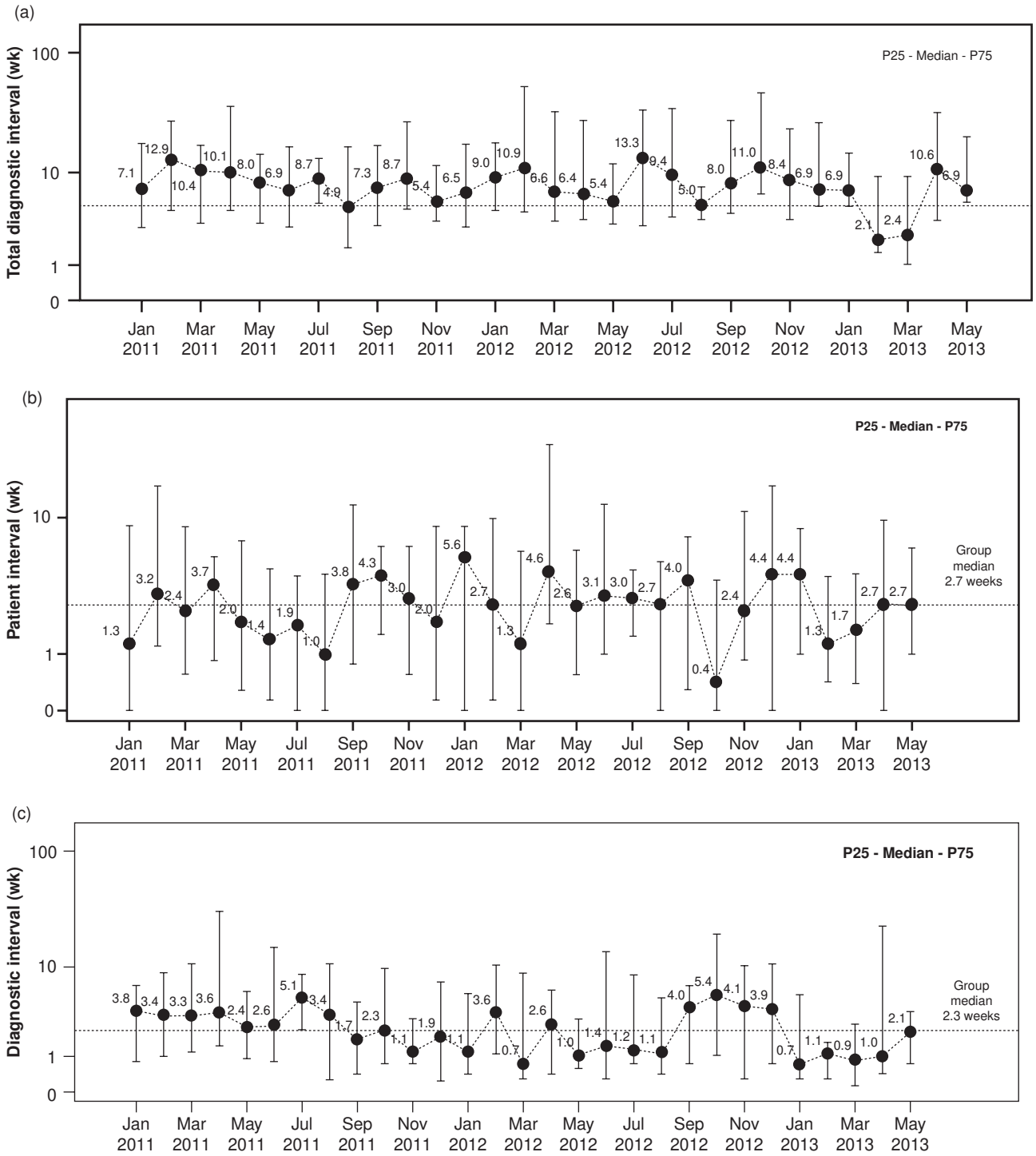


Figure 3.14 Monthly run charts of all patients diagnosed from 6 months before HeadSmart campaign launch (January 2011) to 2 years post-launch (May 2013) and a comparison across three time periods. (a) Total diagnostic interval, time from symptom onset to diagnosis; (b) patient interval, time from symptom onset to first presentation to healthcare professionals; (c) diagnostic interval, time from first presentation to healthcare to diagnosis; (d) comparison across three time periods. (Reproduced from HeadSmart [2016],[15] under Crown Copyright.)

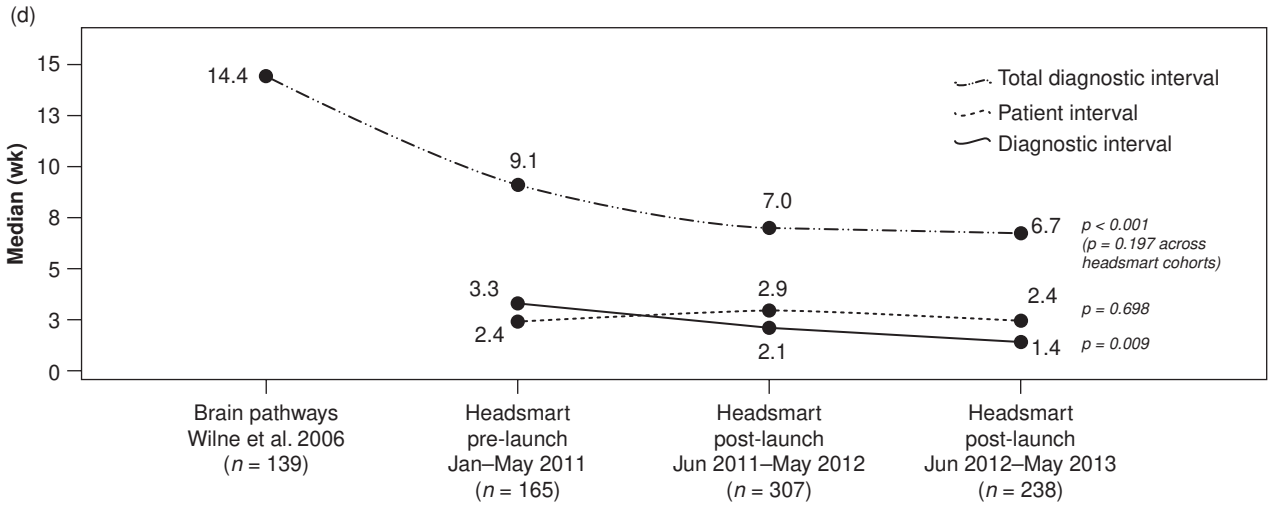


Figure 3.14 (cont.) Monthly run charts of all patients diagnosed from 6 months before HeadSmart campaign launch (January 2011) to 2 years post-launch (May 2013) and a comparison across three time periods. (a) Total diagnostic interval, time from symptom onset to diagnosis; (b) patient interval, time from symptom onset to first presentation to healthcare professionals; (c) diagnostic interval, time from first presentation to healthcare to diagnosis; (d) comparison across three time periods. (Reproduced from HeadSmart [2016],[15] under Crown Copyright.)

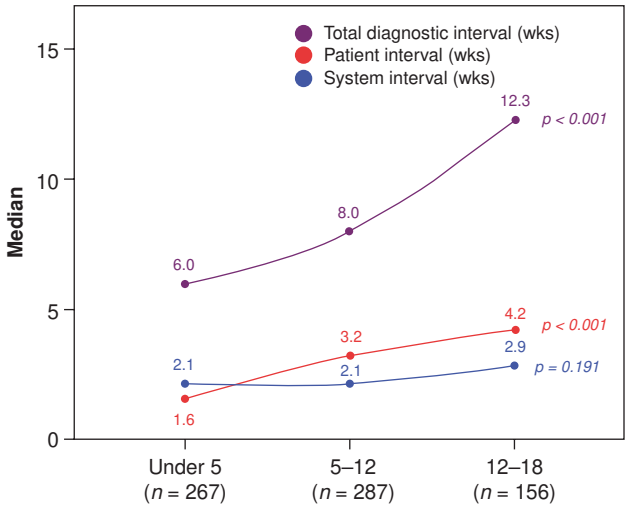


Figure 3.15 Total diagnostic interval, patient interval, and system interval by age group. (Reproduced from Shanmugavadivel et al. [2019],[32] with permission.)

3.15 HEADSMART AWARENESS CAMPAIGN (THE BRAIN TUMOUR CHARITY)

Like any awareness campaign, HeadSmart is wholly reliant on an audience. We need people to hear our message, absorb that message, and pass it on. We can and do use presentations and information leaflets to reach out to specific groups such as GPs and teachers but there is no budget for large-scale paid-for promotion. So how do we go about reaching large numbers of people without prohibitive costs?

The simple answer is: "As healthcare leaders, we need the courage to make a personal stand for what is right. We need to make a profound connection with the deep-seated values that brought us and our colleagues into healthcare in the first place."[33]

The more often HeadSmart and pediatric brain tumor symptoms are mentioned in news outlets and on social media, the higher the number of people who are likely to read or hear about the campaign and its purpose. And the more who do so, the better the odds that any one of those people will recall HeadSmart and those same symptoms when it matters most—when a teenager's headache becomes intractable; when a 4-year-old falls repeatedly and vomits regularly on waking; when a baby tilts its head persistently for no obvious reason.

That's when we want an alarm bell to ring, prompting an online search which leads either directly to the HeadSmart website, or ends up there via a news story that mentions HeadSmart. But news outlets and magazines rarely cover campaigns purely for the public good. They want stories about people, not about abstract issues. So to attract mainstream and social media attention, we need to show HeadSmart's real and potential impact on individual children and families.

That's why we've put people's personal experiences—"human interest stories," in journalism terms—at the heart of our HeadSmart media strategy. To give just one example:

> *Daniel Bell was 3 years old when he experienced symptoms including vomiting, lethargy, and balance problems. His mother Rosalind recalled seeing an image of the HeadSmart symptoms card on Facebook and as a result sought medical advice which led to her son's brain tumor diagnosis. The family shared their story in support of HeadSmart through both regional and national media and in 2017 took part in a BBC TV Lifeline fundraising film for The Brain Tumour Charity which focused on early diagnosis and Daniel's recovery.*

At the other end of the spectrum are the parents who have lost a child to a brain tumor and will never know what earlier diagnosis might have meant. Some of them have been courageous and selfless enough to talk about what they have been through, in support of HeadSmart. Overall, our experience is that many families whose lives are affected in any way by a brain tumor diagnosis want to help others by raising awareness of the disease and its symptoms. When HeadSmart was relaunched in January 2017, for example, dozens of families agreed to lend their

Table 3.2 Key results of the pre-launch professional baseline surveys (March/April 2011) and post-launch follow-up survey (November2011–February 2012)

	Baseline survey (*n* = 323)	Follow-up survey (*n* = 340)
Area of medicine practiced	• Pediatrician, 68% • GP, 24% • Emergency medicine, 1.2% • Other (general surgery, pediatric intensive care unit, nursing, anesthetics), 5.3% • Not known, 0.9%	• Pediatrician, 67% • GP, 20% • Emergency medicine, 0.9% • Other (pediatric surgery, oncology, radiology, neurosurgery, hematology, psychiatry, nursing), 12.4%
Confidence in ability to recognize when a child might have a brain tumor	• 32% of pediatricians were confident • 11% of GPs were confident	• 54% of pediatricians were confident • 12% of GPs were confident
View on the average symptom interval of children in the UK	• <3 months: 37% • 3–4 months: 46% • ≥5 months: 17%	
Respondents' opinion on the statement: "A prolonged symptom interval in childhood brain tumors is associated with worse outcome"	• Increased cognitive deficits: 97.6% agreed • Visual loss: 94% agreed • Endocrinopathies: 87% agreed	• Increased cognitive deficits: 96.5% agreed • Visual loss: 95.3% agreed • Endocrinopathies: 91.2% agreed
Symptoms that could be a sign of a childhood brain tumor (identify from a list of 15 symptoms; may or may not be specifically related to brain tumor)	• Over 95% of GPs and pediatricians thought headache, vomiting, and seizures could be potentially indicative of brain tumor • 53% of GPs thought abnormal head position could be a sign compared with 84% of pediatricians	• Over 95% of GPs and pediatricians identified headache and/or vomiting, deterioration in balance or coordination, change in behavior, seizures or fits, and visual abnormalities as indicators of brain tumor • 53% of the GPs recognized abnormal head position, compared with 98% of pediatricians
Respondents' opinion on: "children with brain tumors have multiple signs and symptoms"	• 91% of GPs agreed • 74% of pediatricians agreed	• 80% of GPs agreed • 75% of pediatricians agreed

Source: Reproduced from HeadSmart Be Brain Tumour Aware (2016),[15] under Crown Copyright.

support to the renewed campaign. This enabled us to target regional media with stories about a young person in their area who had been affected by a brain tumor and who was now throwing his or her weight behind the revamped HeadSmart campaign. In return for these stories, we asked that news outlets carry a link to the HeadSmart website, to ensure more information about the campaign was easily accessible to readers.

We also strive to share the HeadSmart message with publications aimed at healthcare professionals and others such as teachers and nursery staff whose roles bring them into regular contact with children and young people. We have written features about HeadSmart for outlets including *Practice Matters*, the *British Journal of School Nursing*, and the Professional Association for Childcare and Early Years. And in addition to these proactive strands of our media strategy, we provide spokespeople from The Brain Tumour Charity to talk about the HeadSmart campaign in response to journalists' requests when they are covering a story about a child or young person diagnosed with a brain tumor. Since 2013, HeadSmart has achieved editorial space and broadcast slots which would have cost more than £5m to buy as advertising space or time. This coverage has reached tens of millions of people not just in the UK but around the world. By 2017, more than one parent in four (28%) said they had heard of HeadSmart[34]—an achievement which we hope will help to save lives and spare children from the long-term damage which can be caused by delays to a brain tumor diagnosis.

3.16 HEADSMART: THE ROLE OF A COMMUNITY CHAMPION

Sacha Langton-Gilks from Dorset, UK, whose son David was diagnosed with medulloblastoma in 2011, used her skills as a mother, writer, and professional teacher of music and performance to distribute HeadSmart materials—posters, symptom cards, and information packs for professionals in an ad hoc way locally. She quickly realized this was ineffective and would take too long given the scale of ignorance in the general public and health professionals on the symptoms of brain tumors and how many children and young people were affected. What was needed was a systematic, sustainable advocacy approach. She focused on getting symptom cards to parents, knowing that their

advocacy would help emphasize the possibility of a brain tumor to primary care practitioners. If the parents had the symptom card and suspected a brain tumor, they would get to their GP quickly and highlight the importance of considering a brain tumor within their differential diagnosis. Doctors in primary care seldom see a brain tumor case during their career. The symptom cards in the hands of a parent would help reinforce the need for onward referral to a hospital or imaging center.

Key to this was the local public health network. The campaign training emphasized that, for a health message to stick, the public needs to hear the message in six or seven different ways. Sacha's local county council addressed this by coordinating distribution of the symptom cards to all primary school bags, with a local media/social media campaign, and with the public backing of a local Member of Parliament (MP). Since then, other local public health teams in England have sent out campaign materials to pharmacies, GP surgeries, and children's centers within their areas. However, promotion of the initiative relies on a local member of the public speaking to their MP to request a meeting with the local public health network and ensuring the materials are distributed.

In 2012 David was running into problems and recognized that he was dying. The family made a YouTube film clip when he was dying to raise awareness. This was distributed through Facebook and Twitter and went viral, leading to national and international media coverage. Other parents and young people started to contact Sacha and she linked them to the campaign, thereby creating a chain of support. Social media enabled Mrs. Langton-Gilks to speak directly from home to other campaigners and health professionals of every type at local and national levels, as well as reaching out to millions online via the WebDocs network of health professionals. Social media also amplified the effect of articles she wrote on different aspects of the campaign and her family's experience.

Lobbying politicians to raise awareness of the unnecessary suffering and preventable deaths in children and young people affected by brain tumors was also essential. UK partner organization The Brain Tumour Charity's Young Ambassadors are very important, as they talk directly to politicians about how having a brain tumor has affected them and what a difference early diagnosis would have made. They designed the revised campaign and shared in its launch and media responses.

Just after her son died, Mrs. Langton-Gilks persuaded the Public Health Minister to contact all local Heads of Public Health about HeadSmart and write to the Department for Education about raising awareness through health education at school. Additionally, the Teenage Cancer Trust charity in the UK had been going into schools with their prevention and awareness programs for well over a decade and they now include the HeadSmart campaign as part of their talk, realizing it is a way to make the campaign sustainable in the long term.

Sustainability of the campaign like HeadSmart is for all new mothers to be aware of brain tumor symptoms. Further advocacy will be needed to sustain awareness. The Royal College of Paediatrics and Child Health with their responsibility for training curricula for children's specialists have integrated the HeadSmart information into paediatricians' training curricula and are seeking to incorporate it into the personal child health record (also known as the PCHR or "Red Book"), which is a health and development booklet provided to parents/caregivers when a child is born and which stores that child's health data. The PCHR is taken by the parents to all health consultations. These impacts were delivered by committed parental and community champions using their personal experience to color the campaigning and give it a human face. We are deeply grateful to all who participated.

3.17 HEADSMART: THE ROLE OF A CLINICAL CHAMPION

In order to raise awareness of brain tumors in children and young people we took the view that it is essential to engage with both the public and health professionals and get the key messages across to the right people in the right way. Each center in the UK that treats children and young people with brain tumors identified a clinical champion to promote and disseminate HeadSmart messaging in their region. Pediatric oncologists rarely diagnose children with brain tumors but receive referrals after imaging has occurred. As the clinical champion it was very important not to lecture or criticize health professionals where diagnostic intervals were prolonged, but to acknowledge that diagnosing brain tumors in this population is extremely challenging. The HeadSmart guidelines were aimed at supporting professionals, in the majority to offer a basis for reassurance when a brain tumor is not likely, offer time limits for observation, and identify which symptom clusters justify imaging referral. It was emphasized that an appropriate referral with a normal scan was an acceptable outcome!

Productive discussions regarding HeadSmart were tailored to the audience using interactive techniques and supportive discussions of actual case histories, to illustrate the difficulties in diagnosis and how HeadSmart principles may improve the time to diagnosis. It was important to acknowledge potential barriers to referral and, for the diagnosis of brain tumors, issues relating to neuro-imaging. This is particularly relevant in more remote and rural areas, where patients may be a significant distance from appropriate imaging facilities, and for very young patients who may require general anesthesia for satisfactory imaging.

In disseminating and discussing HeadSmart it was essential to reach a broad audience. The HeadSmart campaign and its materials have been extremely well received by medical staff, including those in primary and hospital care, and by allied health professionals, including nursing, physiotherapy, occupational therapy, and opticians. It was also important to engage with professionals outside the healthcare system who interact with children and young people. With this in mind several HeadSmart sessions with staff in education were conducted given their position to

observe when signs and symptoms first appear and their barometric appreciation of what is "normal."

Clinical champions played an essential role in data collection in specialist centers as the HeadSmart program relies on recording accurate TDI from patients when they present. The campaign network across the UK achieved a >70% response rate, providing a representative dataset from which to direct the campaigns. The reward of being able to demonstrate a reduction in the median TDI down from 14.4 to 6.5 weeks was shared by all involved and remains a sustained new improved standard of care in 2018.

3.18 HOW LONG SHOULD IT TAKE TO MAKE A DIAGNOSIS OF BRAIN TUMOR?

In focus group discussion about referral intervals with public and professional groups, the *expectation* of current practice closely mirrored the *actual* practice but differed significantly from the *reasonable* practice expected for a friend or relative. This gap between the *expectation* and *reasonable* practice interval became the focus for the media campaign. At the beginning of the HeadSmart campaign the *actual* TDI across the UK was about 3 months, whilst practitioners, when asked, felt that *desirable* interval to be no more than a month. During the campaign this gap was seen to close. Our working theory was that we had reset the expectations for practice by describing evidence-based symptom clusters and identifying the importance of the cumulative impact of multiple delays by promoting time-limited guidance statements about referral, review, and reassurance. We shared the challenge across the public and professional communities in a sustained program using Quality Improvement performance data to refine the population subgroups to focus the campaign messages. In the early period we successfully communicated with pediatricians and parents of the younger age groups (0–12 years); in the later period we focused the messages on GPs and the adolescent and young adult groups (12–25 years).

3.19 INTERNATIONAL INITIATIVES

There are signs of international interest in studying the intervals associated with brain tumor diagnosis across health systems. This has been stimulated by the gradually growing number of publications studying this phenomenon in brain tumors in particular. The following reports have been contributed by our contacts.

3.19.1 Argentina

In Argentina the Pediatric National Cancer Registry (ROHA) was established in 2002 and it stimulated an all-cancer-types workshop program, including a program titled "When to suspect cancer in children," targeting audiences in the healthcare community. The National Pediatric Cancer Program of the National Cancer Institute runs workshops throughout the country with the Argentine Society of Pediatrics; the material is on the website of the National Cancer Institute, including the topic of brain tumors. In 2018 the HeadSmart material was translated into Spanish and presented in poster format with images made available for training materials. At this early stage evaluation indicated there have been significant improvements in survival rates over three time periods (2000–2004: 3-year survival 63.1%; 2005–2009 3-year survival 68.4%; 2010–2014 3-year survival 72.4%). In 2018 the registry commenced registration of TDIs as part of the registry process from most oncology units. These data will start to describe trends in referral practice, to be monitored prospectively.

3.19.2 Jordan

In Jordan at the King Hussein Cancer Center (KHCC) in 2018 a national project was initiated with the goals to decrease time from first symptoms to first MRI/CT, to decrease the number of subspecialties seen before the first scan, to shorten time to referral to KHCC (as a local referral center with expertise), and to raise public and medical awareness about pediatric central nervous system tumors. The project recognizes the challenges in that there are no previous data on referral times in Jordan to be used as a reference. The national health system does not have a unified data source to record progress through the clinical contact points and so referral will depend upon patient recall. Clinical contact and referral pathways are diverse and there are no guidance documents of recognized pathways disseminated. A key factor is the type of insurance for first contact point selection; and there is also an acknowledged cancer "fear" or "stigma" in the community which may inhibit willingness of families to seek scans or to visit specialist services. The strength of the proposal is that 70–80% of pediatric central nervous system tumors in Jordan are seen in the national center and a further 10–15% are seen in a second "military" hospital.

3.19.3 South Africa

The South African Children's Tumour Registry (SACTR), one of the few of its kind in Africa, was established by the oncology community in 1987, and the community emphasizes early diagnosis of clinical disease by trying to educate healthcare providers and parents.[35,36] In the South African context, it is well known that late diagnosis can compromise outcomes. Local research[37] has shown that interventions can increase ascertainment and may improve the proportion of early diagnoses. Following the profiling of HeadSmart at the International Symposium on Pediatric Neuro-Oncology (ISPNO) in Liverpool in 2016, it was decided to highlight the campaign at the annual Paediatric Brain Tumour Workshop (PBTW), which looks at all aspects of care for children with brain tumors and focuses each year on different aspects of multidisciplinary management of pediatric brain tumors. The meeting profiled the history of HeadSmart and the rationale for profiling early-warning signs for babies, children, and teens, as well as showing some of the literature detailing its outcomes (three excellent abstracts from ISPNO[38–39] and a review in *Paediatrics and Child Health*[41]). The presentation was very well received. HeadSmart material was distributed and attendees promised to advocate amongst health professionals (both GPs and specialists) in their centers.