Beyond Survival - Cognition after Pediatric Brain Tumor

Tonning Olsson, Ingrid

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INGRID TONNING OLSSON
FACULTY OF SOCIAL SCIENCES | DEPARTMENT OF PSYCHOLOGY | LUND UNIVERSITY

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Ingrid Tonning Olsson

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Faculty opponent
Professor Ann-Charlotte Smedler
Psykologiska institutionen, Stockholms universitet

Advisors
Sean Perrin and Aki Johanson

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Abstract

Background: Pediatric Brain Tumor (PBT) survivors suffer from cognitive sequelae, especially within the areas of cognitive tempo, attention, executive function and memory. The cognitive difficulties are often accentuated over the years, but knowledge about the long term trajectory is still scarce.

Aim: The aim of this thesis was to examine cognitive sequelae after Pediatric Brain Tumor (PBT); risk factors, common difficulties, development and neuroimaging correlates.

Methods: In study I, data from medical logs were used to examine characteristics of the patients who got access to neuropsychological services, compared to those who did not. In study II, data from 70 neuropsychological assessments were used to describe common cognitive impairments and to find risk factors. In study III, patients were invited to a follow-up study 10-13 years after diagnosis. Neuropsychological and neuroimaging data were collected and the two were compared. In study IV, longitudinal cognitive data from 173 patients were analyzed in order to describe development over time and to find risk factors for a negative development.

Results: Study I: There were few differences between referred and non-referred patients. Study II: Patients had generally suppressed IQ and difficulties with executive function, memory, cognitive processing speed and attention. Risk factors were Whole-Brain Radiation Therapy (WBRT), large tumors, young age at diagnosis and male sex. Study III: Radiated as well as non-radiated patients had white matter abnormalities. Correlation between neuroimaging and cognition was low when group based statistics were used, but increased when a personalized method was used. Study IV: Most cognitive abilities showed a decline in age related scores over time unconsidered treatment given. Risk factors for impaired cognitive function at diagnosis were: male sex, WBRT, supratentorial lateral tumor, young age at diagnosis, larger tumor size and treatment with chemotherapy.

Conclusions: A systematic neuropsychological follow-up is important. Risk factors for cognitive impairment and IQ decline are WBRT, large tumors, young age at diagnosis, male sex, supratentorial lateral tumor, and treatment with chemotherapy. A decline in IQ after PBT is common, unconsidered treatment given. Personalized methods of research would contribute significantly to our understanding of cognitive sequelae after PBT and its relation to neuroimaging.

Key words: Pediatric Brain Tumor, Cognition, Late sequelae, Cranial Radiation Therapy, Neuropsychology

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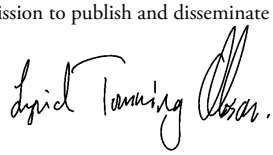
Signature  Date 150928

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Ingrid Tonning Olsson

LUND
UNIVERSITY

Faculty of Social Sciences, Department of Psychology

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List of Studies Included in the Thesis

Study I

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Study II

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Study III

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Study IV

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Abbreviations

AD/HD:	Attention Deficit/Hyperactivity Disorder
ALL:	Acute Lymphoblastic Leukemia
BRC:	Brain Reserve Capacity
CI:	Cognitive Impairment
CMS:	Cerebellar Mutism Syndrome
CNS:	Central Nervous System
COG:	North American Children's Oncology Group
CRP:	Cognitive Remediation Program
(C)RT:	(Cranial) Radiation Therapy
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders, Fifth Revision
DTI:	Diffusion Tensor Imaging
DWI:	Diffusion Weighted Imaging
FA:	Fractional Anisotropy
FDI:	Freedom from Distractibility Index
FLAIR:	Fluid Attenuated Inversion Recovery
(FS)IQ:	(Full Scale) Intelligence Quotient
ICCC-3:	International Classification of Childhood Cancer, Third Edition
ICD-10:	International Classification of Diseases, Tenth Revision
IDD:	Intellectual Developmental (Disability) Disorder
IICP:	Increased IntraCranial Pressure
M:	Mean
MLM:	Multilevel Linear Modeling
MRI:	Magnetic Resonance Imaging
NF:	NeuroFibromatosis

NLD:	Nonverbal Learning Disorder
NSS:	Neurological Severity Score
PBT:	Pediatric Brain Tumor
PNET:	Primitive NeuroEctodermal Tumor
POI:	Perceptual Organization Index
PSI:	Processing Speed Index
SCT:	Sluggish Cognitive Tempo
SD:	Standard Deviation
SIOP-E:	International Society of Pediatric Oncology – Europe
SS:	Standard Score
TMT:	Trail Making Test
VCI:	Verbal Comprehension Index
VCTB:	Vårdplaneringsgruppen för Centrala Tumörer hos Barn
VP shunt:	Ventriculo-Peritoneal shunt
WBRT:	Whole Brain Radiation Therapy
WHO:	World Health Organization

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To Sven, my love of my life You are a part of me!

Introduction

Until relatively recently, children and adolescents diagnosed with a Pediatric Brain Tumor (PBT) had less than a 40% chance of surviving the first 24 months after diagnosis (Madanat-Harjuoja, Pokhrel, Kivivuori, & Saarinen-Pihkala, 2014). For those who did survive past 24 months there remained a significantly increased risk of the tumor(s) returning. Not surprisingly given the risk of death for children with PBTs, the focus was heavily on aggressive medical treatment. Relatively little attention was paid to the impact of the PBTs (or treatment) on survivors' long-term development and psychosocial care needs.

Owing to improvements in early diagnosis and treatment survival rates today are above 70%, albeit with large variations dependent upon the type and location of the tumor (Lannering et al., 2009). A consequence of this dramatic increase in survival rates is that researchers have begun to track the longer-term impacts of PBTs and treatment on the child's development and to try and anticipate and plan for the child's psychosocial and rehabilitation needs. Of particular interest to this research program is the emerging body of literature on the long-term cognitive sequelae of PBTs.

Every year in Sweden approximately 70 children below 18 years of age are diagnosed with a brain tumor and the annual incidence is 4.2/100 000 children (Lannering et al., 2009). Thus each year 50 young people join a growing population of brain tumor survivors in need of rehabilitation and neuropsychological services. Those survivors' needs are the main driving force behind this thesis and research both of which are funded by the Swedish Childhood Cancer Foundation.

Cancer is a word laden with strong negative emotions for most people and when it comes to *children* with cancer it also elicits strong feelings of sympathy and care-taking. After PBT treatment most pedagogues and health care providers are willing and eager to help the survivor; however knowledge and understanding of the cognitive difficulties are often lacking since PBT is such a rare disease. Already in 1976 Bamford et al. (1976) in a study pointed out that:

> "Unless teachers are fully informed and assured about prognosis they are often unwilling to insist on reasonable academic effort, with unfortunate consequences for the child's career. In short, a lack of adequate rehabilitation following therapy may lead to preventable disability" (p1151).

Research focusing on cognitive development after PBT is a relatively new area starting in the early 1980's. It has grown considerably since then but much still remains under-studied including the identification of risk factors for cognitive sequelae, the long-term trajectory of cognitive changes and how these interact with cognitive rehabilitation and overall adjustment. Cognitive rehabilitation after PBT needs to be done in close cooperation between the family, the healthcare team and the school. As part of this process, a neuropsychologist needs to communicate clear information on, and understanding of, the specific cognitive impairments (both subtle and overt) that can arise in connection with PBTs and what help should be offered. To be able to do this more research is needed.

The aims of this thesis are to study risk factors for, and biological correlates of, cognitive sequelae and to study the long term cognitive trajectory. Another aim is to evaluate the neuropsychological support given. Rehabilitation and emotional aspects are beyond the scope of this thesis. It should be said though, that the emotional aspects are equally important and that no rehabilitation could be done without taking them into account (Morton & Wehman, 1995).

A Spectrum of Diseases

There is significant heterogeneity associated with PBTs. Tumors may be of many different types and occur in one or multiple locations. There is wide variation in when the PBTs are first diagnosed as well as in the types of treatments available that can be delivered in combination or in a serial fashion. Pediatric brain tumors also occur in children with pre-existing genetic, neurological and behavioral disorders. This heterogeneity among children identified in medical settings with PBTs presents significant challenges to researchers attempting to specify the risks for, and long-term trajectory of, cognitive sequelae in PBT survivors.

Heterogeneity in Tumor Type and Localization

Pediatric brain tumor (PBT) is not a disease, it is several. Tumors in the brain originate from different types of cells and are classified thereafter in six different sub-categories according to the 3rd Edition of the International Classification of Childhood Cancer, (ICCC-3)(Steliarova-Foucher, Stiller, Lacour, & Kaatsch, 2005). The most common PBT is astrocytoma affecting around 45% of the diagnosed patients followed by medulloblastoma/PNET (Primitive NeuroEctodermal Tumor) at 19% and ependymomas at 10%. Approximately 14% have other specified neoplasms, e.g. craniopharyngeoma (a tumor growing in and above the pituitary gland) (Lannering et al., 2009). Tumors are classified into different grades of malignancy (tendency to grow and spread) rated from 1 to 4 with 1 being the least malignant. The pre-clinical PBT research is at present at the threshold of shifting focus from histopathologic classifying to the different molecular

pathways that underpin tumors. For example, what would previously have simply been categorized as medulloblastoma/PNET based on histopathology alone can be now broken down into four separate categories according to histopathology and molecular biology, each with a given prognosis (Sadighi, Vats, & Khatua, 2012).

A brain tumor, per definition, is located within the skull but the cognitive effects of a tumor partly depend on the localization of the tumor within the brain. Approximately half of PBTs are situated below the tentorium and the initial symptom is usually hydrocephalus with morning nausea, vomiting or headaches (Wilne, Dineen, Dommett, Chu, & Walker, 2013). The location of supratentorial tumors can roughly be divided into two categories: lateral/cortical and midline. The initial symptoms of cortical tumors are usually epilepsy or focal neurological deficits and initial symptoms of midline tumor are usually hormonal deficiencies, vision impairment, or hydrocephalus (Reulecke, Erker, Fiedler, Niederstadt, & Kurlemann, 2008).

Heterogeneity in Treatment

There are four main treatment options available to patients with PBTs: no further medical intervention; surgery; chemotherapy; and radiation therapy. A minority of patients receive no medical intervention beyond diagnosis and monitoring, primarily patients with neurocutaneous syndromes where the tumors might be discovered very early before symptom onset and where tumors are known to be benign. Approximately half of all PBT patients receive surgery only and the remainder surgery plus chemotherapy and/or Cranial Radiation Therapy (CRT). Surgery only is usually given to patients with low grade gliomas with no or small residual tumors after surgery and to patients with low grade and/or supratentorial ependymomas with no residual tumors. Each of the treatments have been shown to have a negative impact on cognition, either as a complication of surgery (Ater et al., 1996; Kao et al., 1994), chemotherapy (especially if it is given directly into the CNS) (Riva et al., 2002), or CRT. Our understanding of how specific treatments impact cognitive functioning remains limited because treatment protocols for PBT patients are continuously evaluated, changed, and new techniques introduced (e.g. better ways of delivering radiation therapy).

In addition to treatment aiming directly at the tumor, PBT patients often receive additional treatments are frequently given for tumor-related conditions, e.g. steroids to alleviate Increased IntraCranial Pressure (IICP), hormone replacement therapy to compensate for hormonal deficiencies, and anti-epileptic drugs to prevent seizures.

Heterogeneity in the Child's Premorbid Conditions

Several premorbid factors influence risk of cognitive sequelae after PBTs, among them the age and sex of the child, socioeconomic status, schooling, genetic syndromes and pre-existing learning difficulties. As regards age at diagnosis, it is very consistently shown that the younger the child the greater risk for cognitive sequelae (Patel, Mullins, O'Neil, & Wilson, 2011; Reimers et al., 2003). Some studies have shown that girls are more vulnerable to cognitive difficulties after a PBT but the literature remains unclear as regards the interaction of gender, tumor type/location, treatment and cognitive sequelae (G. T. Armstrong, Sklar, Hudson, & Robison, 2007).

Learning disabilities are quite common in the general population, affecting 8-9 % of all children (Patel et al., 2014). In general it is recognized that PBTs may aggravate existing learning disabilities. Children with pre-existing genetic conditions, e.g. neurofibromatosis, have learning difficulties with much higher frequency compared to the normal population and it is likely that these difficulties are aggravated by the tumor and its treatment (De Winter, Moore, Slopis, Ater, & Copeland, 1999; Moore, Ater, Needle, Slopis, & Copeland, 1994; Ullrich, 2008). On the other hand, it is also true that a child who has managed to cope with learning difficulties present prior to diagnosis may cope better with any emerging, tumor-related cognitive impairments but this requires further investigation.

Background

Early Studies

The development of research on cognitive sequelae following PBTs was examined in an early systematic review by Glauser and Packer (1991). The authors found that if one relied upon studies carried out in the late 1960's and 1970's where school performance and global disability rating scales (as opposed to neuropsychological tests) were used as outcome measures, then between 9% and 60% of PBT survivors were cognitively 'disabled' and/or were receiving special education. The first study involving systematic use of standardized neuropsychological assessment of cognitive sequelae was carried out by Hirsch, Renier, Czernichow, Benveniste, and Pierre-Kahn (1979). Glauser and Packer (1991) note that once standardized neuropsychological assessments of PBT survivors became more common, research on this patient group suggested that the actual rate of cognitive sequelae was between 40 and 100%. It is important to note that even prior to this shift to neuropsychological assessment of cognitive sequelae, and prior the development of modern neuroimaging techniques, early researchers (cf., Bamford et al., 1976) postulated that the cognitive sequelae were likely multi-factorial in origin with vascular changes caused by radiotherapy being a likely culprit for the observed cognitive sequelae. This theory is still considered valid today (Duffner, 2010). Over time, studies of cognitive sequelae have

become more focused: studying the effects of one type of tumor; focusing on one aspect of cognitive ability; comparing cognitive deficits in different treatment groups; and identifying brain regions vulnerable to CRT (G. T. Armstrong et al., 2010).

Factors Correlated with Cognitive Sequelae

Despite the availability of studies suggesting that cognitive sequelae after brain tumors were multi-determined, many early studies focused almost exclusively on the potential detrimental effects of medical treatments – particularly CRT (Hoppe-Hirsch et al., 1995; Jannoun & Bloom, 1990). This research led to important changes in cancer treatment protocols but contributed to a wider view that the field needed to broaden its focus from 'who's to blame?' to the broader array of likely risk factors (C. L. Armstrong, Gyato, Awadalla, Lustig, & Tochner, 2004; Glauser & Packer, 1991).

Several quantitative meta-analyses have now been undertaken that strongly suggest that cognitive sequelae arise from biological factors like the tumor itself and the treatment given (including surgery) as well as from psychosocial factors including the child's premorbid ability, socioeconomic status and the interaction between the child and his/her environment (De Ruiter, Van Mourik, Schouten-van-Meeteren, Grootenhuis, & Oosterlaan, 2012; Robinson, Fraley, Pearson, Kuttesch, & Compas, 2013; Robinson et al., 2010). The majority of the studies have been cross-sectional or retrospective in nature and found the following variables to be correlated with cognitive outcomes: age at diagnosis, treatment given, gender, hydrocephalus and/or placement of ventriculo-peritoneal (VP) shunt, surgery complications, recurrences, localization of tumor, genetic conditions, tumor in itself, gender, epilepsy and non-cognitive sequelae secondarily affecting cognitive function (De Ruiter et al., 2012; Robinson et al., 2010, 2013). Two of the meta-analyses report on the much fewer studies available that involved methodologies (longitudinal and/or with control groups) that permitted estimation of actual "risk" and found that CRT, treatment with chemotherapy, longer time since diagnosis and younger age at diagnosis were significantly associated with negative cognitive sequelae following diagnosis with a PBT (De Ruiter et al., 2012; Robinson et al., 2013).

Low Age at Diagnosis/Treatment

Across studies of PBT survivors, young age at diagnosis is consistently shown to be a risk factor for cognitive sequelae (Dennis, Spiegler, Hetherington, & Greenberg, 1996; Mulhern et al., 2001; Reimers et al., 2003; Sands et al., 2012; Vinchon, Baroncini, Leblond, & Delestret, 2011). This is also true for most pediatric neurological disorders (e.g. traumatic brain injury and epilepsy) (Garcia, Hungerford, & Bagner, 2014; Vasconcellos et al., 2001) Such findings have prompted a debate (still ongoing) about the plasticity versus vulnerability of the young brain, however most researchers now see both aspects as present and interacting (V. A. Anderson, Spencer-Smith, & Wood, 2011) or even as two sides of the same coin. For example some have argued that the young brain's vulnerability to insult

(e.g. brain tumors) may result from a lack of equilibrium between plasticity and homeostasis, i.e. the young brain may be "too plastic" since plasticity in itself is not positive or negative (Dennis et al., 2013).

The vulnerability of the youngest children to cognitive sequelae following PBTs might also be explained by their lack of premorbid acquired knowledge. Abilities like memory, attention, tempo and executive function are often affected by a PBT and its treatment, and such impairments might obstruct further acquisition of new knowledge resulting in declining skills compared to same-age peers (Dennis, Ross Hetherington, & Spiegler, 1998).

Cranial Radiation Therapy

Cranial Radiation Therapy (CRT) is one of the most well-studied risk factors for cognitive sequelae in PBT survivors. Meta-analyses have consistently shown CRT increases the risk of negative cognitive sequelae (De Ruiter et al., 2012; Robinson et al., 2013). Cognitive sequelae are seen both during CRT treatment, 6-12 weeks after treatment (early delayed), and as a process continuing several years after treatment (C. L. Armstrong et al., 2004; Moore, 2005). Changes during treatment and the immediate aftermath (6-12 weeks) are considered transitory and are beyond the scope of this thesis.

Several factors are thought to moderate the risk for cognitive sequelae associated with CRT, specifically: Whole Brain Radiation Therapy (WBRT) has been shown to be more detrimental than focal CRT (Ellenberg, McComb, Siegel, & Stowe, 1987; Fuss, Poljanc, & Hug, 2000; Hoppe-Hirsch et al., 1995); higher doses are more detrimental than lower doses (Merchant, Kiehna, Li, Xiong, & Mulhern, 2005); and the temporal lobes, hypothalami and hippocampi are more vulnerable to damage (G. T. Armstrong et al., 2010; Dennis et al., 1992; Merchant, Schreiber, et al., 2014; Redmond et al., 2013). Several studies have shown that local radiation to the posterior fossa region is associated with stable or better cognitive outcomes (Grill et al., 1999; Hoppe-Hirsch et al., 1995; Merchant et al., 2006; von Hoff et al., 2008), however one recent study examining ependymoma patients, treated with focal radiation only, found a negative correlation between radiation dose to the cerebellum and cognition (Merchant, Sharma, Xiong, Wu, & Conklin, 2014).

Not surprisingly given the above literature, treatment protocols for PBT are subject to regular scrutiny and change with one aim being the prevention of cognitive sequelae, e.g. by postponing CRT for younger children and/or limiting the radiation field (Merchant et al., 2005) and dose (Kieffer-Renaux et al., 2005), and incorporating new interventions such as proton beam therapy (Macdonald et al., 2013).

Chemotherapy and Other Medications

Very few studies have examined the impact on cognition of chemotherapy alone on PBT patients. Where it has been examined the studies have been focused primarily on the potential benefits of replacing radiotherapy (RT) with chemotherapy in very young children diagnosed with medulloblastoma or ependymoma, using RT only as a second-line

treatment in case of recurrence. Of interest to this research, those studies reported normal IQ in patients treated with chemotherapy alone (Ater et al., 1997; Rutkowski et al., 2009). Fouladi et al. (2005) conducted a similar longitudinal study with a much larger sample of PBT patients diagnosed at age three or less. Chemotherapy was given to all patients, but CRT was given only at recurrences or a year after diagnosis if the tumor was highly malignant. They found cognitive improvement over time in PBT patients treated with chemotherapy only, while patients receiving RT (focal or WBRT) showed a decline. However, even if patients treated with chemotherapy only did not decline, the rate of severe Intellectual Developmental Disorder (IDD) was 20% in this group, i.e. markedly higher than in a normal comparison sample.

Studies on patients with Acute Lymphoblastic Leukemia (ALL) and other types of cancer (not just of the brain) have found evidence of subtle but stable negative effects on cognitive sequelae arising from chemotherapy alone (F. S. Anderson & Kunin-Batson, 2009; Copeland, Moore, Francis, Jaffe, & Culbert, 1996; Moleski, 2000; von der Weid et al., 2003) although not always (cf., Riva et al., 2009). Studies examining the impact of chemotherapy used together with CRT have shown an additive negative effect of chemotherapy on cognitive outcomes (Bull, Spoudeas, Yadegarfar, Kennedy, & CCLG, 2007; Di Pinto, Conklin, Li, & Merchant, 2012; Mitby et al., 2003; Netson, Conklin, Wu, Xiong, & Merchant, 2013; Riva et al., 2002). There is preliminary evidence that the type of chemotherapy used and where it is administered (directly into CNS or intravenously) might also play a role since the permeability of the blood-brain barrier differs between substances (F. S. Anderson & Kunin-Batson, 2009).

In addition to chemotherapy, PBT patients often receive other types of medication: steroids for treatment of IICP, anti-epileptic drugs for preventing seizures and hormone replacement therapy to name a few. [Anti-epileptic drugs and seizures are discussed under the heading epilepsy below.] Hormone deficiencies may arise as a direct consequence of tumors located in the pituitary and/or hypothalamic regions and/or as a late consequence of radiation to central parts of the brain (Merchant, Conklin, Wu, Lustig, & Xiong, 2009). Dennis et al. (1992) found a correlation between hormonal deficiencies and cognition related to age but also pointed out the difficulties in separating the effects of different hormonal deficiencies and hypothalamic injury. Conklin, Li, Xiong, Ogg, and Merchant (2008) found pre-existing endocrine deficits and lower growth hormone levels at diagnosis to be correlated with a steeper decline in reading scores after CRT.

Hydrocephalus and Ventriculoperitoneal Shunt

Approximately half of all PBTs are found in the posterior fossa region of the brain (Farwell, Dohrmann, & Flannery, 1977). Tumor growth in this area impinges upon the cerebral aqueduct causing IICP and related symptoms like nausea and vomiting, headaches, as well as vision and motor disturbances. Increased ICP or hydrocephalus (the more permanent condition) is associated with cognitive impairment in general (Hampton et al., 2013; Lumenta & Skotarczak, 1995). Several studies have shown it to increase the risk of cognitive sequelae in PBT patients (Di Pinto et al., 2012; Hardy, Bonner, Willard, Watral, &

Gururangan, 2008; Merchant et al., 2004; Reimers et al., 2003), while other studies have not found this correlation (E. E. Davis, Pitchford, Jaspan, McArthur, & Walker, 2011). Hydrocephalus is usually treated with placement of a ventriculo-peritoneal (VP) shunt or ventriculostomy and studies have found that VP shunting increases the risk of cognitive sequelae (G. T. Armstrong et al., 2010; Merchant, Schreiber, et al., 2014; Netson, Conklin, Wu, Xiong, & Merchant, 2012; Willard et al., 2013). However a study by Aarsen et al. (2009) involving patients with pilocytic astrocytoma found that ventricular dilation (one measure of IICP) was related to cognitive impairment while treatment with a VP shunt resulted in better cognitive outcomes. In a longitudinal study assessing IQ and three different measures of ventricular volume, Merchant et al. (2004) found that patients with larger volumes pre-CRT had lower IQ scores but experienced an improvement in IQ over time. The rate of improvement was correlated with a reduction in ventricular size leading the authors to conclude that some of the detrimental cognitive effects may be reversible and that fast and adequate treatment of hydrocephalus is necessary.

Pre-, Peri- and Postoperative Complications and Recurrences

Techniques and instruments for carrying out intracranial surgery are constantly being improved and thereby lowering, but not eliminating, the risk of neurological complications. In an important early study Kao et al. (1994) 23 children with medulloblastoma/posterior fossa primitive neuroectodermal tumors were followed repeatedly with neuropsychological tests after surgery and treatment with radiation (with or without chemotherapy). The authors found that in addition to other risk factors that repeated surgeries were associated with marked and significant declines in IQ. In another early study, Ater et al. (1996) created a "Neurological Severity Score" (NSS) to try and capture the pre- peri- and post-surgery neurological factors the might influence cognitive functioning. The NSS was based on the presence and severity of seizures, mental status changes, pre-existing learning disabilities, postoperative fever or hormonal complications, postoperative slow recovery, poorly controlled seizures, and mutism. Based on data collected from 59 children with astrocytomas (both supra- and infratentorial) who had complete neurological and neuropsychological evaluations within 3 months of diagnosis, Ater et al. (1996) found that NSS scores correlated significantly and negatively with scores on the neurocognitive measures. They argued that cognitive deficits in brain tumor patients were the result of cumulative insults to the CNS. More recent studies have confirmed that neurological complications (Moxon-Emre et al., 2014) and recurrences and multiple surgeries are significantly associated with negative cognitive outcomes (Conklin et al., 2008; Di Pinto, Conklin, Li, Xiong, & Merchant, 2010).

Cerebellar Mutism Syndrome (CMS) is a specific complication that can arise after surgery on the posterior fossa region of the brain (Gudrunardottir, Sehested, Juhler, Grill, & Schmiegelow, 2011; Korah et al., 2010). CMS affects up to 24% of children with medulloblastoma (Robertson et al., 2006). The child with CMS seems to recover well in the first days after surgery but then goes into a state characterized by linguistic, neurobehavioral and motor impairment. The symptoms can be quite severe and might

involve paralysis, severe ataxia, mutism or emotional instability with apathy, whining or pathological crying. CMS is transitory, lasting a few days up to several months, with some symptoms being persistent and/or taking a milder form (Huber, Bradley, Spiegler, & Dennis, 2006). The pathogenesis of CMS is unclear but damage to cerebello-thalamo-cortical connections have been proposed, either as direct damage or by diaschisis (Miller et al., 2010). Several studies have identified CMS as a predictor of late cognitive sequelae (De Smet et al., 2009; Huber et al., 2006; Palmer et al., 2010; Schreiber et al., 2014).

Tumor Localization

Acquired brain injuries in children have different consequences than similar injuries in adults, since the child's brain is developing "around" the injury (V. A. Anderson, Northam, Hendy, & Wrennall, 2001; Dennis et al., 2013). In children, even if the brain injury is focal the cognitive consequences are often less focal and not directly linked to tumor localization. In spite of this, several studies have found a correlation between tumor localization and cognitive sequelae in children but with wide variation in the level of association. Ellenberg et al. (1987) and Jannoun and Bloom (1990) found children with hemispheric tumors tended to be more vulnerable to negative cognitive outcomes. Patel et al. (2011) found no differences between patients with supra- and infratentorial tumors in measures of general cognitive functioning, but that the presence of infratentorial tumors was correlated with deficits in academic achievement, working memory and parent-reported behavioral functioning and anxiety. Ris et al. (2008), in a study examining extracerebellar low-grade PBTs, found that patients with tumors in the left hemisphere were more vulnerable to cognitive sequelae but observed no differences in cognitive outcomes based on hemispheric, midline or brainstem localization of the tumors. However other studies have found midline localization of the tumor (and especially hypothalamic involvement) to be correlated with poorer cognitive outcomes (Danoff, Cowchock, Marquette, Mulgrew, & Kramer, 1982; Fjalldal et al., 2013).

It was generally believed that patients with low-grade posterior fossa tumors only receiving surgery were at least risk for negative cognitive sequelae, however several recent studies have found a relationship between cerebellar localization and later cognitive and behavioral deficits (Beebe et al., 2005; Cantelmi, Schweizer, & Cusimano, 2008; Grill, Viguier, et al., 2004). Those authors have stressed the role of cerebellum in cognitive and behavioral regulation.

Genetic (neurocutaneous) Syndromes

As mentioned before the two most common genetic syndromes associated with an increased risk for PBTs are neurofibromatosis 1 and 2 (NF1 and NF2) and tuberous sclerosis (Ullrich, 2008). For example, Wong et al. (2005) examined the case records of 986 Taiwanese children referred for treatment of PBTs over a 12-year period and found 3.5% to have a pre-existing phacomatosis, i.e. a congenital disorder characterized by benign tumor-like growths found in the CNS (mainly NF1/2 and tuberous sclerosis). Tuberous sclerosis is associated with subependymal giant cell astrocytomas. NF1 is associated with optic nerve

gliomas and NF2 with acoustic neuromas, usually low grade tumors in all cases. Both tuberous sclerosis and NF1/2 are significantly associated with learning disabilities, somewhat more so for tuberous sclerosis (Hyman, Shores, & North, 2005; Winterkorn, Pulsifer, & Thiele, 2007). In an attempt to separate the cognitive effects of neurofibromatosis from PBT, Moore et al. (1994) compared scores on measures of intelligence and academic achievement of 14 children with NF1 only, those of two age-matched comparison groups of children (14 each) with PBT only or both NF1 and PBTs. All examinations were done after surgery (in case) but before any additional treatment. Children in the PBT only group had the highest IQ and achievement scores followed by those in the NF1 and NF1+PBT groups. In a later study, De Winter et al. (1999) compared the cognitive functioning of 36 children with NF1 only to a matched sample of children with NF1 plus a PBT and found no differences between groups except when those in the NF1 group were compared to a subgroup of 9 children in the NF1+PBT group who had received cranial radiation.

Tumor Itself

It might seem intuitive to conclude that the tumor itself generates cognitive impairment, and more so if the tumor is larger. Studies examining neuropsychological status before treatment for a PBT are scarce, often because the time between diagnosis and surgery is usually short and PBT patients are often too unwell physically and emotionally to undergo extensive neuropsychological evaluation. In one of the few studies to examine this issue, Brookshire, Copeland, Moore, and Ater (1990) examined pre-treatment neuropsychological assessments in 31 PBT patients. Cognitive functioning was within normal limits for all tested areas except for a subgroup with anterior hemispheric tumors who had pre-treatment deficits in executive cognitive functions. The presence of supratentorial midline and infratentorial tumors was associated with lower scores on tests of fine motor and visual-motor skills. Iuvone et al. (2011) studied 83 PBT patients before treatment and found IQ at diagnosis to be within normal limits although with a higher percentage of patients with an IQ below 70 than expected from norms. All patients with IQ below 70 had a tumor in temporomesial structures. In this study the only factors correlated with cognitive performance were symptom duration before diagnosis and epilepsy. Children with cortical tumors showed the worst performance in all measures and size of tumor did not predict cognitive performance (Iuvone et al., 2011)

Brasme et al. (2012) examined 166 medulloblastoma patients to see if longer time from symptom onset to diagnosis (using initial tumor size as a measure of diagnostic delay) was associated with worse neuropsychological outcomes. They concluded, quite contrary to intuition, that larger tumor size at diagnosis was correlated with better neuropsychological outcomes; the authors arguing that other factors than diagnostic delay predicted the neurocognitive outcome, i.e. tumor malignancy.

What can be inferred from the above literature, aside from the need for more studies including those involving prospective designs, is that the impact of the tumor itself on

overall cognitive ability prior to treatment appears less important than other pre-treatment risk factors except for a subgroup of patients with focal cognitive deficits.

Sex

It is quite often mentioned in the literature that girls are more vulnerable to cognitive sequelae after PBT treatment than boys (Butler & Haser, 2006; Moore, 2005; Wolfe, Madan-Swain, & Kana, 2012). However in a review of the literature, G. T. Armstrong et al. (2007) conclude that such a view is only (tentatively) supported for patients with ALL, and that there is a lack of consistent evidence that girls are more vulnerable to the cognitive effects of PBTs than boys. Longitudinal studies published after this review have continued to yield disparate results on the relationship between cognition and sex in PBT survivors. For example two large studies by Di Pinto et al. (2012) and Netson et al. (2013) found that girls were at increased risk for steeper declines in cognitive abilities than boys, while Merchant, Schreiber, et al. (2014) found being female predicted lower baseline IQ. By way of contrast Ris et al. (2013) found no sex differences in the cognitive trajectories of boys or girls after diagnosis and treatment of a PBT. One study has even found that being male was associated with an increased risk for a decline in reading scores after CRT (Conklin et al., 2008), while another study, assessing partly the same patients, showed being male was a predictor of improved cognitive performance after CRT (Di Pinto et al., 2010).

Epilepsy

Epilepsy occurs in approximately 25% of long-term PBT survivors, 6.5% of whom had onset for the condition more than 5 years after diagnosis of the PBT (Packer et al., 2003). Epilepsy is most often associated with the presence of cortical tumors and with the use of CRT on supratentorial brain areas increasing the risk for late-onset epilepsy. Epilepsy itself has a complex relationship to cognitive difficulties, the relationship influenced by three main factors: etiology of the epilepsy; frequency of seizures; and use of anti-epileptic drugs (AEDs) (Aldenkamp, Baker, & Meador, 2004). Poor seizure control is associated with worse cognitive outcomes as is treatment with high doses of AEDs and/or poly-drug therapy (Ortinski & Meador, 2004).

While epilepsy has long been recognized as a commonly occurring complication of PBTs (and treatment of the same), relatively few studies have examined their impact on cognitive functioning in PBT patients. Macedoni-Luksic, Jereb, and Todorovski (2003) examined the cognitive functioning of 61 long-term survivors of PBTs and found that 13 (21%) had epilepsy, the presence of which was associated with the presence of a supratentorial tumor. Nearly half of all the patients (44%) fell in the mild to severe range of Intellectual Disability Disorder (IDD), with epilepsy being the strongest risk factor for IDD, poorer educational attainment and unemployment. Iuvone et al. (2011) examined cognitive functioning prior to treatment in 83 children with newly diagnosed brain tumors and found that the duration of PBT symptoms and the presence of epilepsy were significantly associated with neuropsychological disabilities. G. T. Armstrong et al. (2011) carried out a long-term study of 361 children diagnosed with low-grade gliomas. Of the 182 children who were

repeatedly assessed for cognitive functioning and who survived five or more years, 34% had an IQ below normal and this negative outcome was strongly associated with the presence of epilepsy, use of a shunt, and age at diagnosis.

Non-cognitive Sequelae Secondarily Affecting Cognitive Abilities

Sensory deficits like auditory and vision impairment and motor disabilities are common after PBTs (E. E. Davis, Pitchford, Jaspan, McArthur, & Walker, 2010; Packer et al., 2003; Schreiber et al., 2014). Vision impairment may be caused by damage to the optical nerve, either by tumor growth or IICP. Auditory problems are common particularly after treatment with the chemotherapeutic agent vincristine or radiation therapy involving the cochlear regions (Whelan et al., 2011). Motor impairments might be focal (e.g. hemiplegia) or global (e.g. polyneuropathia or general ataxia which is common after cerebellar tumors). Sensory and motor deficits can in turn aggravate cognitive difficulties and impair academic performance and progression, e.g. ataxia can make hand writing extremely difficult, requiring concentrated efforts, and thereby leaving less working memory/attention available for the academic task.

In addition to sensory/motor deficits, CRT can increase the risk of vascular diseases like Moyamoya syndrome (constriction of arteries in the brain) and stroke which in turn increase the risk for negative cognitive sequelae (Baumgartner et al., 2003; Duffner, 2010; Gurney et al., 2003). In fact some authors have proposed vasculopathy as one of the primary process underlying white matter deficits and late-emerging cognitive deficits in PBT survivors (Reddick et al., 2014).

Social Factors, Coping Strategies and Rehabilitation Given

Each PBT patient and family copes with this condition in different ways and some coping strategies might be associated with poorer cognitive outcomes, e.g. by parents and caregivers demanding too little or too much from the child (Hocking et al., 2011). A review of this literature is beyond the scope of this thesis but is important to state that family structure/functioning and access to adequate rehabilitation services are associated with long-term cognitive and behavioral outcomes after diagnosis of a PBT (Ach et al., 2012; Butler et al., 2008; Callu et al., 2008; Carlson-Green, Morris, & Krawiecki, 1995; Hardy, Willard, Allen, & Bonner, 2012).

Relating the Cognitive Difficulties to the Underlying Biological Mechanisms

In the beginning of the 1980's, studies linking cognitive sequelae more directly to underlying biological processes as neuroimaging technologies became more common. Damage to and/or slow development of white matter was identified as a possible cause of negative cognitive sequelae. White matter damage in relation to cognition has been measured and quantified with several different neuroimaging techniques, e.g. counting hyperintensities, calcifications and atrophy (C. L. Armstrong et al., 2002; P. C. Davis,

Hoffman, Pearl, & Braun, 1986; Fouladi et al., 2004; Iuvone et al., 2002), measuring areas of abnormalities (Doolittle et al., 2013), volumetric measures (Jacola et al., 2014; Mulhern, White, et al., 2004; Reddick et al., 2014) and more recently using diffusion tensor imaging (DTI) (Khong et al., 2006; Rueckriegel, Bruhn, Thomale, & Hernáiz Driever, 2015). Studies using volumetrics have shown reduced white matter volume with a stagnating or decreasing development of white matter volume (as opposed to the age-related increases in volume expected in normal children)(Reddick et al., 2000). Studies using DTI have found lower Fractional Anisotropy (FA) in several major tracts, e.g. the genu of corpus callosum, the internal capsule and in frontal lobe white matter (Aukema et al., 2009; Mabbott, Noseworthy, Bouffet, Rockel, & Laughlin, 2006; Palmer et al., 2012).

Correlations between cognition and all the above mentioned white matter measures have been established in most studies and brain abnormalities have been mostly attributed to CRT. However three recent studies by Rueckriegel et al. (2010), Liu et al. (2014) and Rueckriegel et al. (2015) find that that patients receiving surgery only for PBT have altered DTI measures similar to patients receiving CRT and chemotherapy but to a lesser extent. It was also shown by C. L. Armstrong et al. (2005) that MRI abnormalities directly after treatment were more prominent in patients treated with surgery alone than in patients treated with surgery together with CRT.

Longitudinal Studies

Early longitudinal studies of PBT survivors found evidence of decreasing IQ over time and, in a very well cited article, Hoppe-Hirsch et al. (1990) even dared to talk about medulloblastoma as a "progressive intellectual deterioration." This conclusion was later modified by Palmer et al. (2001) who argued that the observed decline in IQs in PBT patients reflected slowed development rather than a true cognitive deterioration. Several large longitudinal studies have now been carried out and most of them confirm an IQ decline with the drop in Full Scale IQ (FSIQ) ranging from 1 to 4.3 standard scores per year (Kieffer-Renaux et al., 2005; Ris, Packer, Goldwein, Jones-Wallace, & Boyett, 2001). Stargatt, Rosenfeld, Maixner, and Ashley (2007) propose different trajectories of cognitive development after PBT with one trajectory for tumor/surgery related injury (IQ worsening first year, then stable) and another trajectory for chemotherapy and CRT-related injury (stable IQ and later decline). Nevertheless most longitudinal studies have used linear models to describe changes in IQ but a few studies have instead used quadratic models with steeper declines in IQ immediately after treatment and then gradually reaching a plateau some years later (Mabbott et al., 2005; Palmer et al., 2003; Spiegler, Bouffet, Greenberg, Rutka, & Mabbott, 2004).

A range of different variables have been shown to be associated with cognitive decline in PBT survivors. The most commonly reported are: WBRT (discussed below), young age at diagnosis (Kieffer-Renaux et al., 2005; Knight et al., 2014; Mulhern et al., 2005), hydrocephalus (Moxon-Emre et al., 2014), higher baseline IQ (Palmer et al., 2013; Palmer

et al., 2003; Ris et al., 2001; Ris et al., 2013) and larger radiation field/higher radiation dose (Mabbott et al., 2011; Merchant et al., 2006). Gender differences have been found with most studies reporting that girls are more vulnerable to cognitive decline (Di Pinto et al., 2012; Kiehna, Mulhern, Li, Xiong, & Merchant, 2006; Ris et al., 2001) while at least one study found the opposite (Conklin et al., 2008).

However marked cognitive decline is most frequently found in pediatric patients with medulloblastomas receiving whole brain radiation treatment (WBRT). Studies examining patients with other types of tumors or patients receiving only focal CRT or reduced-dose WBRT have found mixed results. For example, in an early longitudinal study Ellenberg et al. (1987) found WBRT, but no other types of treatment, to be related to cognitive decline. Examining attentional abilities among patients receiving focal conformal CRT, Kiehna et al. (2006) found only one of four measured aspects of attention to decline after CRT even if attentional abilities were depressed from baseline. Di Pinto et al. (2010) found stable or improved learning performance after localized conformal radiation therapy. Netson et al. (2012; 2013) found stable cognitive performance in ependymoma, craniopharyngeoma and lowgrade glioma survivors. By way of contrast, two studies have found declining academic abilities in patients with low grade gliomas (Conklin et al., 2008; Merchant et al., 2009).

Developmental Models Describing Cognitive Changes after PBT

Schatz, Kramer, Ablin, and Matthay (2000) were some of the first to propose a neuropsychological model to understand cognitive late sequelae after treatment with CRT in patients with ALL. They argued that CRT mainly impacts processing speed which in turn leads to decreases in IQ mediated by working memory deficits. Reddick et al. (2003) developed a slightly different model relating cognitive sequelae to white matter deficits caused by treatment of the PBTs. In their study of 40 PBT survivors they found a significant correlation between white matter volumes; full-scale IQ (FSIQ) and academic achievement, and they hypothesized that this relationship was mediated by deficits in attention and memory. Path analyses confirmed that attention deficits, but not memory deficits, mediated the relationship between white matter and FSIQ/academic achievement. This model was further developed by Palmer et al. (2008; 2007), Wolfe et al. (2012) and Askins and Moore (2008) who argue that the cancer treatment disrupts white matter development which in turn causes core cognitive deficits in attention, working memory, executive function, and cognitive processing speed which in turn impact IQ and academic attainment.

In contrast to the above models is the concept of diminished Brain Reserve Capacity (BRC) (Satz, 1993) as applied to brain tumor survivors (Edelstein et al., 2011). Brain Reserve Capacity is thought of as the brain's ability to maintain function after an injury or in normal aging. The reserve capacity is a threshold up to which the brain can adjust. If the total brain stressors (injuries, intoxications, aging etc.) exceed this threshold it causes severe impairment. A large BRC can be seen as resiliency factor while a smaller might be seen as

a vulnerability factor. A brain tumor and then treatment for the same might constitute a considerable reduction of BRC leaving PBT patients vulnerable to future brain stressors like normal aging (Edelstein et al., 2011).

Several authors (Peterson & Drotar, 2006; Rey-Casserly & Meadows, 2008) have argued that explanatory models of cognitive impairment in PBT survivors need to better address family and school factors, the child and family's coping responses, and to view the child as the center of an interacting system, e.g. a child sustaining a brain injury puts different demands on her/his parents, who in turn, affect their child's development with their behavior. They also point out the need to consider both the developmental stage of the child when injured and the nature of interventions offered at different ages. The models of cognitive change in PBT survivors described above make mention of additional mediators such as whether the child has received rehabilitation and the extent of the child's individual resources but do not fully address the kind of factors suggested by Peterson and Drotar (2006) or Rey-Casserly and Meadows (2008).

Common Cognitive Sequelae

The type of cognitive sequelae an individual PBT survivor experiences is likely to be multi-determined and involving all of the risk factors mentioned above. Nevertheless some commonalities exist in terms of the cognitive sequelae reported: lowered IQ (often decreasing over time), and impairments in cognitive processing speed, attention, memory, executive function, academic achievement and social skills.

Lowered IQ

Most studies have used IQ as a measure of cognitive function, most often measured by an age-appropriate Wechsler test (Wechsler, 2005). Since IQ is a compound of several different abilities it is not surprising that almost all studies have found lowered and/or declining IQ. The cognitive profile most often reported in PBT survivors is one with better verbal abilities, lower results on non-verbal abilities, and scores on measures of working memory and processing speed most affected (Grill et al., 1999; Kieffer-Renaux et al., 2000; Poggi et al., 2005). Some authors have proposed the concept of a Nonverbal Learning Disability (NLD) to be useful in this population. Patients with NLD have better verbal than nonverbal abilities, poor visuospatial processing, and impairment in arithmetic and social skills – a profile which also describes PBT survivors (Bonner, Hardy, Willard, & Gururangan, 2009; Buono et al., 1998; Carey, Barakat, Foley, Gyato, & Phillips, 2001).

Cognitive Processing Speed

One of the most frequently found impairments in PBT survivors is slow cognitive processing tempo (Kahalley, Conklin, et al., 2013; Mabbott, Penkman, Witol, Strother, & Bouffet, 2008). Together with impairments in working memory, executive function and

attention, post-treatment change in these four processes are seen as the core impairment in several of the models described in the chapter above.

Attention

Compared to children with Attention Deficit/Hyperactivity Disorder (AD/HD) or children with traumatic brain injuries, PBT survivors show a different pattern of attention deficits. They are more often inattentive, fail to notice relevant stimuli and cannot sustain attention (Briere, Scott, McNall-Knapp, & Adams, 2008; De Ruiter et al., 2012; Dennis et al., 1998). It has been pointed out by Kahalley et al. (2011) that children with attention difficulties after PBT do not meet the general criteria of AD/HD. Some authors have described the attention problems after PBT as more similar to the subset of AD/HD symptoms called Sluggish Cognitive Tempo (SCT) (Reeves et al., 2007; Willard et al., 2013). This AD/HD subgroup is characterized by slow tempo, poor executive function, lethargy and day dreaming.

Memory

Pediatric BT patients experience memory deficits in several areas including working memory (Knight et al., 2014), as well as verbal and non-verbal declarative memory, and immediate and delayed recall (King et al., 2004; Micklewright, King, Morris, & Morris, 2007; Reimers et al., 2003).

Executive Function

Executive function is a broad concept comprising abilities like planning and organizing, shifting, self-monitoring, problem solving and metacognition. Since working memory and attention are often included in the concept of executive functioning it is not surprising that PBT survivors are frequently found to have executive deficits, but general executive difficulties have also been found (i.e. impairment in shifting, categorizing and verbal fluency) (Brinkman, Reddick, et al., 2012; Maddrey et al., 2005; Spiegler et al., 2004).

Academic Achievement

Several studies have examined academic achievement in PBT survivors and found difficulties mainly in reading, writing and math (Reddick et al., 2003). Like IQ, those skills have been reported to decline over time after diagnosis (Mabbott et al., 2005; Ris et al., 2013). Two studies have identified reading abilities as the most vulnerable (Conklin et al., 2008; Schreiber et al., 2014) while others have found math abilities to be more vulnerable (Bonner et al., 2009; Robinson et al., 2013). Overall, it appears that PBTs and their treatments have a greater impact on tests of academic achievement than neuropsychological measures as partly evidenced by studies that have found declines in academic achievement in PBT survivors even when IQ decline is absent or limited (Fouladi et al., 2004; Merchant et al., 2009).

Social Skills

Several studies have found PBT survivors to have deficits in social skills and pro- social behaviors as well as fewer friends (Fiona Schulte & Barrera, 2010; Schultz et al., 2007). Externalizing problems like aggression or oppositional behavior are less common than internalizing behaviors (avoidance/withdrawal) and problems (anxiety/depression) (Mabbott et al., 2005). Holmquist and Scott (2002) examined the association between behavior in PBT patients and found long-term verbal memory problems and general learning problems predicted internalizing behaviors. Social skills in PBT patients have also been linked to difficulties with face recognition. Bonner et al. (2008) showed PBT survivors to have impaired face recognition skills even when general IQ was controlled for. The authors also point out that social competence requires fast cognitive processing and understanding of subtle visual cues, areas in which PBT survivors are known to have deficits.

Methods

Patients

All patients in the four studies described in this thesis were assessed and treated for PBTs at the Department of Paediatrics based in Skåne University Hospital. The department serves a large geographic region with approximately 1.7 million inhabitants (the total population of Sweden being approximately 9 million during the course of the study). All samples are population based, i.e. all PBT patients living in the region are treated at this center. Types of cancer, gender ratio and survival rates are similar to those of the whole population of PBT patients diagnosed in Sweden with the sample reported here representing 15% of this population (Lannering et al., 2009). Patients included in study I-III were to a very large extent neuropsychologically examined and treated by the author of this thesis, Ingrid Tonning Olsson (ITO). In study IV all examinations were done either by ITO or by a colleague supervised by her. At 18 years of age all patients were transferred to adult health care and were no longer followed at the Department of Paediatrics and were lost to further follow-up.

Neuropsychological services have been offered at the department since 1995. Until 2006 neuropsychological examinations were done solely on a referral basis. In 2006 a grant from the Swedish Childhood Cancer Foundation made it possible to start a neuropsychological screening program and neuropsychological examination was offered to all diagnosed patients at the following time points: just before surgery (where possible) 1, 3 and 5 years post diagnosis and at 18 years of age. The screening program was started to more fully evaluate the effects of treatments, to identify patients in need of further psychosocial support, and to comply with Swedish and international recommendations on the neuropsychological screening of PBT patients. The first four time points for assessment were chosen in accordance with recommendations of a national Swedish protocol for assessment of PBT patients. A further neuropsychological examination was added at 18 years of age was added so that any current cognitive sequelae were documented before transfer to adult services.

At the start of this project, a retrospective investigation was carried out on all PBT patients seen in the department between 1995 and 2006. The purpose of the investigation was to identify how many had been referred for a full neuropsychological examination and to compare the results of these examinations to similar data available from published reports of PBT patients both in Sweden and internationally. Patients surviving less than a year were

excluded from the investigation since they were almost always too sick to undergo a neuropsychological evaluation. As a result of this investigation it was discovered that roughly half of the PBT patients were subsequently referred for a neuropsychological examination (n=64) while the remainder were not referred (n=68). This meant that around the time of diagnosis for PBT, clinicians were or were not aware of potential cognitive deficits in at-risk group and then either did or did not refer the young person for neuropsychological evaluation. The purpose of Study I was to determine whether any differences existed between the referred and non-referred groups as any such difference might point to a referral bias and if the two groups were similar, would provide evidence in support of a policy of routine referral for neuropsychological evaluation.

The purpose of Study II was to evaluate the relationship between neuropsychological test results and various patient (age, sex, age-at-diagnosis, tumor type etc) and treatment variables. For these analyses, subjects who had got at least one complete neuropsychological examination were included (n=69). Study III, included a subsample of PBT patients (n=16) who had agreed to participate in a pilot investigation involving neuropsychological examinations and an MRI scan using Diffusion Tensor Imaging (DTI). The purpose of the study was to explore whether the DTI would yield biological correlates to any cognitive sequelae. Study IV is longitudinal and includes all data collected as part of the routine neuropsychological screening program that began in 2006, as well as all available clinical data collected prior to this program (n=173, measurement points=433). In this study the trajectory of cognitive difficulties was examined and related to known risk factors.

During the period from which data was collected (retrospectively and prospectively) for those 4 studies (1993-2013) a total of 300 patients were diagnosed with PBTs with 275 of these surviving more than one year. Thus the participants in Studies II-IV (n=215) represent 78% of all patients diagnosed with a PBT and surviving more than one year over this 21-years period.

Literature Search

The literature search was done continuously from year 2000 forward via searches of the Pub Med central database and Google Scholar using words like “pediatric”, “brain tumor” and “cognition”. References were also collected using the “snowball technique” with inclusion of references in read articles in the database. Over the years over 500 articles on cognition after pediatric brain were recorded, including reviews.

Statistical Methods

Several different statistical methods were used for the four studies, all using SPSS versions 20-23 (IBM, 2011). Representativeness was analyzed using Student's t-test for continuous variables and χ^2-tests for categorical variables in all studies. Multivariate statistical models were used in Study II and IV, linear regression models in the former and multilevel linear models in the latter. In Study III, two different methods of analysis were used, one quantitative, group based and one qualitative personalized. Those two methods were then compared.

Terminology

Throughout this thesis the terms "cognitive impairment" and "cognitive sequelae" are used interchangeably. Different terms are used for "mental retardation". Mental retardation is a term still used in the tenth edition of the World Health Organization's (WHO) International Classification of Diseases (ICD-10) but it will most probably be replaced by "Intellectual Developmental Disorder" (IDD) in ICD-11. In the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5), mental retardation has been replaced by Intellectual Disability (Disorder), shortened ID(D). ICD-10 and DSM-5 use a somewhat different terminology but the same abbreviation (Harris, 2013; Salvador-Carulla et al., 2011). In this thesis the term IDD is used with the exception of Study I and II. In Study I the term "Cognitive impairment with an IQ <70" is used, and in Study II the older term "mental retardation" is used.

Ethical Considerations

Study I, II and IV made use of anonymized data originally collected from patients with PBTs for clinical purposes at the Department of Paediatrics, Skåne University Hospital in Lund. The gathering, analyses and publication of these anonymized clinical data were approved by the Lund University ethical committee (Dnr 2013/68). The gathering, analysis and publication of neuroimaging and clinical data collected for Study III from PBT patients either currently or formerly registered with the department was approved as part of a separate ethics application (Dnr 500/2007).

Study I. Access to Neuropsychological Services After Pediatric Brain Tumor

Background

Children treated for Pediatric Brain Tumors suffer from cognitive sequelae. Well identified risk factors for cognitive impairment are young age at diagnosis, treatment with Cranial Radiation Therapy (CRT) and periods of Increased IntraCranial Pressure (IICP). In several studies it is concluded that a systematic recording of cognitive abilities is needed to evaluate treatment, not only in terms of survival but in terms of quality of survival and cognitive sequelae (Moxon-Emre et al., 2014; Robinson et al., 2013). A systematic neuropsychological follow-up is also essential for finding patients in need of rehabilitation and to stratify the help given, i.e. offer individualized rehabilitation. Clinical and research guidelines are published by The North American Children's Oncology Group (COG) (Nathan et al., 2007; Noll et al., 2013), and by the International Society of Paediatric Oncology Europe (SIOP-E) (Limond et al., 2015) and there is a national protocol accepted by the Swedish Working Group for Paediatric Central Nervous System Tumors ("Vårdplaneringsgruppen för CNS-tumörer hos barn," (VCTB) 1993). All those guidelines recommend systematic neuropsychological follow-up. However, implementation of those guidelines has proven difficult for several reasons, lack of neuropsychological resources being one of them (Embry et al., 2012). When neuropsychological resources are scarce the most common way to handle it is to examine only a subgroup of patients on a referral basis. The aim of this study is to evaluate this routine.

Purpose

To evaluate rates of referral by medical doctors to neuropsychological services and patient and treatment factors that differentiated referred and non-referred patients.

Methods

A population based sample of patients diagnosed during 12 years and surviving more than a year (n=132) was analyzed retrospectively. The following variables were compared between the referred and nonreferred groups: age at first diagnosis; sex; treatment; classification and localization of tumor; size of the tumor at diagnosis; death within the study period; IICP at diagnosis; ventriculoperitoneal shunt or ventriculostomy; neurocutaneous syndromes; medication; epilepsy; and cognitive impairment measured with either neurocognitive tests (referred patients) or with schooling as a proxy (non-referred patients).

Results

Half of the diagnosed patients had been referred for neuropsychological services with the most common reasons being a parent, teacher or member of the medical team observing cognitive difficulties. Few differences between the referred and nonreferred groups were found (Table 1). The referred group had larger tumors and more often IICP at diagnosis and had had more recurrences. Twenty-two percent of the nonreferred patients had cognitive difficulties indicated in their medical records. There were no differences between the groups in the prevalence of potential risk factors for cognitive impairment (e.g. patients receiving CRT or with young age at diagnosis).

Table 1.
Characteristics of referred and non-referred patients

	Examined patients, n=64	Not examined patients, n=68	Total group, n=132	p value
Girls	34	24	58	0.053
Average age at first diagnosis	8.14	8.98	8.57	0.31
Astrocytoma	30	40	70	0.22
Treatment given				
Surgery	60	61	121	0.53
Chemotherapy	24	17	41	0.14
Locally admin. CRT	37	28	65	0.081
Whole brain RT	11	7	18	0.31
Average size of tumor at diagnosis (widest diameter)	3.85cm	3.10 cm	3.46 cm	0.015
Increased ICP at diagnosis	39	23	62	0.003
Deceased at the end of year 2006	5	9	14	0.40
One or more relapses	28	15	43	0.010
Neurocutaneous syndromes*	5	9	14	0.40
Ventriculo-peritoneal shunt or ventriculostomy	11	8	19	0.46
Epilepsy	7	8	15	1.00
Medication				
Hormone replacement therapy	22	20	42	0,58
Anti-epileptic drugs	8	11	19	0.62
Infratentorial/supratentorial tumor	33/31	28/40	61/71	0.30
Cognitive impairment, IQ<70	8	8	16	0.84
Cognitive impairment, IQ<80	8	7	15	

* 11 pts with Neurofibromatosis I, 2 pts with Neurofibromatosis II, 1 pt with tuberous sclerosis

Discussion

This is the first study to evaluate neuropsychological referral practices with respect to PBT survivors. The results shows few differences between the PBT patients who were and were not referred for neuropsychological evaluation, Relative to non-referred patients, those who were referred did suffer somewhat more frequently from factors associated with an increased risk of cognitive sequelae (i.e., larger tumors, IICP, recurrences of tumors). However among the non-referred group were patients with well-known risk factors for cognitive sequelae (e.g. young age at diagnosis, WBRT, existing cognitive difficulties). It was not possible in this study to determine whether the parents of PBT patients were unhappy when their child was not referred for neuropsychological evaluation or even whether such a referral was needed. Hoven, Lannering, Gustafsson, and Boman (2011) carried out a survey of 526 adult survivors of CNS tumors and their parents and found that 41% reported that their requests for health care, particularly in the domain of psychosocial services went unmet. The present findings highlight why guidelines governing neuropsychological evaluation recommend that *all* children diagnosed with a PBT be referred for repeat neuropsychological screening (Limond et al., 2015; Nathan et al., 2007; Noll et al., 2013), i.e. all children diagnosed with PBT should be considered at increased risk of cognitive sequelae (often late-emerging). While Swedish clinical guidelines recommending systematic neuropsychological follow-up after PBT have been available during the main part of the studied time period, greater efforts are needed to disseminate, implement and ensure compliance to existing recommendations.

Conclusions

A systematic neuropsychological follow-up is crucial both for the patient to receive support and rehabilitation and for evaluating changes in cancer treatment, not only in terms of survival, but in term of quality of life. Greater efforts are needed to disseminate and raise awareness about published guidelines on the long-term care of PBT patients.

Study II. Long-term Cognitive Sequelae after Pediatric Brain Tumor Related to Medical Risk Factors, Age, and Sex

Background

PBT survivors are substantially increased risk of a broad range of negative cognitive sequelae, particularly deficits in cognitive processing speed, attention, memory and executive functioning (Askins & Moore, 2008; Knight et al., 2014; Willard et al., 2013). When considering risk for such deficits, early longitudinal studies of PBT survivors concentrated on the effects of CRT. Later studies have looked at a broader range of risk factors and concluded that in addition to CRT, young age at diagnosis, hydrocephalus, longer time since diagnosis, and neurological complications all interact to increase the survivors risk of cognitive sequelae (Moxon-Emre et al., 2014; Robinson et al., 2013; Schreiber et al., 2014). Some studies (Ellenberg et al., 2009; Ris et al., 2001) have suggested that girls may be more at risk than boys for cognitive sequelae but at least one substantive review of the relevant literature suggested that the available data are far too limited to draw any firm conclusions (G. T. Armstrong et al., 2007). Recently published findings from the Childhood Cancer Survivor Study which involves the long-term follow-up of 6,139 survivors of pediatric CNS tumors, leukemia, lymphomas and sarcomas found that girls were at increased risk of a range of more negative psychosocial outcomes that the authors attributed to an increased burden of disease on girls (Prasad, Hardy, Zhang et al., 2015). The authors did find a slightly increased risk of memory problems for girls over boys but the results were based on analysis of the children who had either CNS tumors or leukemia, the latter form of cancer being having been found to be independently associated with a greater risk of cognitive impairment in previous reviews of the literature (Armstrong et al., 2007). In addition patients with PBT might have underlying genetic conditions like neurofibromatosis or tuberous sclerosis that can cause brain tumors as well as learning difficulties (De Winter et al., 1999).

Between 1995 and 2006 neuropsychological services was offered at a referral basis at Skåne University Hospital. In this study we wanted to retrospectively review all assessments done during this period and replicate and expand upon earlier long-term studies of risk factors for cognitive sequelae in PBT survivors.

Purpose

To find factors correlated with lowered IQ in a nationally representative sample of PBT patients referred for neuropsychological evaluation.

Methods

Over a 12 year period (1995 to 2006), a total of 112 PBT patients were referred to the Neuropsychology Clinic in the Department of Pediatrics at Skåne University Hospital. Of these, 40 had received only a short interview or a short pre-surgery screening and were excluded from the analyses in this study. One further patient who had severe intellectual disabilities and was assessed with a neuropsychological test that was not age- appropriate was also excluded. This left 69 patients who were referred and who had undergone at least one neuropsychological evaluation involving age-appropriate standardized tests of cognitive functioning, and these patients comprised the current sample.

All data were collected from the medical and neuropsychological records. Coded variables were age at diagnosis, sex, classification and localization of tumor, size of the tumor at diagnosis, neurocutaneous syndromes, epilepsy, treatment type, hydrocephalus at diagnosis and use of ventriculoperitoneal shunt or ventriculostomy (Table 2). In addition to recording test results the neuropsychological reports were reread and any cognitive difficulties that were mentioned were recorded for subsequent analysis.

Stepwise multiple linear regressions were used to find factors associated with cognitive impairment and a sub-analysis was made of the covariation of sex and tumor size. Difficulties mentioned in the neuropsychological reports were categorized and counted.

Table 2.
Characteristics of the Study Group (n=69)

	Average/freq.	Std. dev.	Range
Girls/Boys	36/33		
Average age at first diagnosis (years)	8.01	4.35	0.81-17.37
Type of tumor, WHO ICCC-III *			
III a, Ependymomas and choroid plexus tumors	10		
III b, Astrocytomas	34		
III c, Intracranial and intraspinal embryonal tumors	9		
III d, Other gliomas	5		
III e, Other specified intracranial and intraspinal neoplasms	11		
Treatment given			
Surgery	63		
Chemotherapy	24		
Locally admin. CRT	40		
Whole brain RT	11		
Average size of tumor at diagnosis (widest diameter)	3.80 cm	1.69	0.9-8.0
Increased ICP at diagnosis	41		
One or more relapses	30		
Neurocutaneous syndromes†, neurofibromatosis or tuberous sclerosis	7		
Ventriculoperitoneal shunt or ventriculostomy	13		
Epilepsy	7		
Infratentorial/supratentorial tumor	35/34		
Average time elapsed between diagnosis and testing (years)	4.58	3.31	0.09-12.79
Average age at testing (years)	12.61	4.07	4.34-20.57

* World Health organization: International Classification of Childhood Cancer, third edition
† 4 pts with Neurofibromatosis I
2 pts with Neurofibromatosis II
1 pt with tuberous sclerosis

Results

The patients had generally suppressed IQ with average scores 0.75-1.0 SDs below mean for the relevant age. Lowest average IQ scores were on Processing Speed Index and highest on Verbal IQ (Table 3). The analysis of the neuropsychological reports showed executive dysfunction, memory difficulties, slow cognitive processing and attention impairment to be the most frequent problems (Table 4). Only four of the referred patients (all girls) had normal cognitive functioning.

The multiple stepwise linear regression analyses showed lowered IQ to be associated with young age at diagnosis, being male, tumor size and treatment with WBRT (Table 5).

Table 3.
Neuropsychological measures, IQ-values with norms mean m=100 and SD=15

	Mean	Stddv	n	Min	Max
Full scale IQ	87.03	21.93	69	37	127
Verbal IQ	90.80	19.08	69	42	126
Performance IQ	85.55	23.76	69	32	144
Verbal comprehension index	91.54	16.16	56	50	120
Perceptual Organization Index	89.25	19.98	55	49	137
Freedom from distractibility	87.02	18.53	55	48	131
Processing Speed Index	82.36	20.25	56	47	147

Table 4.
Problems mentioned in the neuropsychological reports

	Number of reports	%
Executive dysfunction	34	49.28
Memory difficulties	34	49.28
Slow cognitive processing	26	37.68
Attention difficulties and/or hyperactivity	25	36.23
Mental retardation/ generally reduced cognitive capacity	14	20.29
Language difficulties	12	17.39
Visuospatial perception difficulties	12	17.39
Academic failures	10	14.49
Reduced fine or gross motor skills	7	10.14
Difficult relationship to others	4	5.80
Emotional difficulties/depression	1	1.45

Table 5:
Linear regression models for different IQ measures

Dependant variable	Expl. variance	Variables included in the model	Unstand. coefficients		Stand coefficients	p
			b	std. error	beta	
Full Scale IQ, n=69	29.8%	(Constant)	84.20	5.52		
		Gender	-12.26	4.55	-.28	.009
		Whole Brain Radiation Therapy	-20.28	6.18	-.34	.002
		Age at first diagnosis	1.49	0.53	.30	.009
Verbal IQ, n=69	29.4%	(Constant)	94.40	6.85		
		Tumor size	-2.65	1.22	-.24	.034
		Whole Brain Radiation Therapy	-17.25	5.47	-.33	.002
		Age at first diagnosis	1.15	0.47	.26	.017
Performance IQ, n=69	25.3%	(Constant)	84.72	6.17		
		Whole Brain Radiation Therapy	-19.68	6.91	-.31	.006
		Age at first diagnosis	1.33	0.59	.24	.027
		Gender	-14.01	5.08	-.31	.008
Verbal Comprehension Index, n=56	27.0%	(Constant)	98.61	2.76		
		Whole Brain Radiation Therapy	-16.39	5.50	-.38	.001
		Gender	-7.89	3.76	-.25	.041
Perceptual Organization Index, n=55	19.0%	(Constant)	97.45	3.61		
		Whole Brain Radiation Therapy	-20.01	7.03	-.36	.006
		Gender	-11.18	4.97	-.28	.029
Freedom from Distractibility Index, n=55	24.6%	(Constant)	77.75	5.51		
		Whole Brain Radiation Therapy	-19.82	6.28	-.38	.003
		Age at first diagnosis	1.43	0.58	.30	.017
Processing Speed Index, n=56	27.0%	(Constant)	92.60	3.44		
		Whole Brain Radiation Therapy	-24.62	7.19	-.41	.001
		Gender	-15.44	4.77	-.38	.002

Stepwise linear regression, backwards entry of variables. Variables removed at p>0.05.
Variables entered at step 1: Age at diagnosis, Chemotherapy, Radiation therapy, Whole brain radiation therapy, Increased IntraCranial pressure (ICP) at diagnosis, Ventricular Peritoneal shunt or ventriculostomy, Gender (female=0, male=1), Tumor size (largest diameter in cm), Astrocytoma, Time between diagnosis and testing.

A covariation was found among the independent variables: boys had larger tumors than girls at PBT diagnosis. This was hypothesized to be caused by boys having larger head circumference, i.e. larger volume of the skull allows a tumor to grow larger before signs of hydrocephalus appear. This hypothesis was supported when patients with and without IICP at diagnosis were analyzed separately concerning tumor size and sex. The covariation between sex and tumor size was also analyzed with simple correlations, a linear regression model including sex and size only, and with the Johnson-Neyman technique for probing interactions in linear models (Hayes & Matthes, 2009). Those analyses showed tumor size to be a better predictor of cognitive sequelae than sex, and sex differences in cognition to be most apparent when tumors were middle-sized, i.e. around 2-3cms.

Discussion

This is one of the larger studies to examine risk factors for cognitive impairment specifically focusing on survivors of PBTs (versus other forms of childhood cancer). The study benefits from a population-based Swedish sample and the use of both quantitative and qualitative measures of cognitive outcomes. It is also the first study to examine the relationship between tumor size and sex in this population. In line with previous research, the patients had generally suppressed IQ and a cognitive profile with better verbal abilities and lowest average IQ scores on tempo and short term memory tasks (Bonner et al., 2009; Spiegler et al., 2004). The analysis of the neuropsychological reports revealed impairments in attention, executive function, cognitive processing speed and memory to be the most common difficulties, which is also in line with earlier studies (Brinkman, Reddick, et al., 2012; Palmer et al., 2013). Four variables were most strongly related to cognitive impairment: WBRT, sex, tumor size and age at diagnosis.

The finding that WBRT, but not focal CRT was related to worse cognitive performance is quite well documented in previous research (Ellenberg et al., 1987; Fuss et al., 2000), however in several earlier studies no distinction is made between the two types of CRT. WBRT is mostly given to patients with medulloblastoma who also receive chemotherapy, making it difficult to separate the cognitive effects of the two treatments. In a previous study by Di Rocco et al. (2010) of 41 patients with posterior fossa tumors, 18 of them medulloblastomas and the rest of them with pilocytic astrocytomas, found that those with medulloblastomas were more likely to have impaired cognitive performance prior to surgery. Untangling the cognitive effects of WBRT from pre-existing cognitive deficits in PBT patients will require focused research methodology and large sample sizes.

Contrary to the findings of some earlier studies (Ellenberg et al., 2009; Ris et al., 2001), but consistent with one critical review of the literature in which no cognitive gender differences in PBT survivors was found (G. T. Armstrong et al., 2007), the present study found that boys were at increased risk of cognitive impairment. Further analyses revealed that this gender-based risk interacted with tumor size and the presence of hydrocephalus.

These are new findings and support the conclusions of Armstrong et al. (2007), that evaluation of gender-based risks for negative outcomes in childhood cancers requires recognition and analysis of underlying biological and physiological bases of sex-specific risks and outcomes.

Conclusions

Whole-brain radiation therapy, large tumors, young age at diagnosis and male gender are risk factors for cognitive sequelae after PBT. When examining sex differences, tumor size at diagnosis needs to be taken into account.

Study III. Relation between Cognitive and Neuroimaging Data in Long-term Pediatric Brain Tumor Survivors

Background

Children surviving PBT often suffers from cognitive sequelae, e.g. slow cognitive processing, memory and attention deficits, related to several treatment and personal factors (Moxon-Emre et al., 2014; Willard et al., 2013). The cognitive sequelae have been related to brain white matter abnormalities in studies applying several different neuroimaging techniques and quantification methods, e.g. counting hyperintensities, calcifications and atrophy (C. L. Armstrong et al., 2002; P. C. Davis et al., 1986; Fouladi et al., 2004; Iuvone et al., 2002), computing areas of abnormalities (Doolittle et al., 2013), using volumetric measures (Jacola et al., 2014; Mulhern, White, et al., 2004; Reddick et al., 2000; Reddick et al., 2014) and more recently using Diffusion Tensor Imaging (DTI) (Aukema et al., 2009; Mabbott et al., 2006; Palmer et al., 2012). The correlations found between cognitive deficits and abnormalities detected by neuroimaging have largely been attributed to the negative effects of Cranial Radiation Therapy (CRT) on brain tissue. However two recent studies, by Rueckriegel et al. (2010) and by Liu et al. (2014) found that PBT patients who had only undergone surgical treatment had altered DTI measures similar to patients receiving CRT and chemotherapy but to a lesser extent.

Purpose

To explore different methods of correlating cognitive and neuroimaging data in PBT survivors, i.e. to evaluate whether congruency between cognitive outcome and morphological MRI measures in PBT survivors differs if these two parameters are analyzed independently or in a personalized multidisciplinary approach accounting for both parameters in conjunction with further clinical data.

Methods

Sixteen pediatric brain tumor survivors completed a neuropsychological test battery and MRI at an average of 12.2 years after diagnosis (range 10.2-13.5 years) and at a mean age of 22.3 years (range 13.0-29.3 years).

Neuropsychological Measures

Forty-three different measures of cognitive function were collected. The neuropsychological test battery was chosen to measure cognitive areas most commonly affected by PBTs: general cognitive reasoning, cognitive processing speed, executive function, attention and memory. In the quantitative evaluation patients were coded as positive or negative for cognitive impairment (CI+ or CI-) with CI+ assigned to patients with ≥ 10% of the 43 neuropsychological variables below 1 standard deviation compared to normal.

Magnetic Resonance Imaging

The MRI protocol included clinical axial none-enhanced T1, T2, fluid attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) as well as contrast enhanced coronal and axial T1 weighted images. MRI studies (pre-treatment MRI and follow up MRI) were evaluated by an experienced neuro-radiologist blinded to clinical data and neuropsychological test results. MRI findings were then assigned a spread score (0-4) for each patient: 0 = no abnormalities or asymptomatic findings not related to tumor or treatment, 1 = focal lesion consistent with location of original tumor or surgery, 2 = lesional and/or peri-lesional abnormalities, 3 = additional abnormalities located beyond original tumor and surgery areas but ipsilateral (on same side) of tentorium, and 4 = additional abnormalities located beyond original tumor and surgery area contra-laterally of tentorium. For the quantitative approach patients were coded as positive or negative for MRI findings (MRI+ or MRI-) with MRI+ assigned to patients with an MR abnormality spread score ≥ 3.

Comparison of Cognitive and Neuroimaging Measures

Two different analysis methods were used to correlate neuropsychological data to MRI findings: 1/ a strictly quantitative approach based on group statistics including cognitive outcome parameters (CI+ or CI-) and imaging data (MRI+ or MRI-); and 2/ a personalized approach combining quantitative with qualitative elements. In the latter personalized approach, quantitative cognitive and imaging data for each patient were reviewed in a multidisciplinary session with a focus on clinically relevant interpretation of these data – categorizing quantitative imaging data as congruent or incongruent with cognitive outcome

for individual patients. The primary clinical data used to personalize imaging and cognitive data were: location and size of lesions in terms of functional instead of anatomical aspects, postoperative status as function of potential disintegration of brain function compared to shire occurrence of post-operative changes, potential treatment effects on brain function and correlation of e.g. radiation field contra affected brain function. Furthermore, data on premorbidity and/or comorbidity were added to the assessment. The synthesis of the quantitative data and clinical interpretation of these data confirmed or disconfirmed the clinical congruency between MRI findings and cognitive outcomes. In a further evaluation, factors contributing to differences in congruency between the quantitative and personalized approach were examined.

Results

Neuropsychology

Mean cognitive measures were close to normal and mean measures for tempo and attention were below normal, with a wider dispersion compared to given norms. In general the distribution of most test results is characterized by a few patients showing impaired performance in a majority of measures while the remaining patients show results comparable or above average in the majority of measures with more focal difficulties. In group analysis, mean results below -1 SD were most often seen on simple tempo tests.

Magnetic Resonance Imaging

In the quantitative analysis ten patients were classified as MRI+ and six as MRI-, i.e. MR abnormality spread score 1 or 2. Bivariate correlations comparing the MRI abnormality spread score with clinical variables did not show any statistically significant correlations (p values ranging from .23 to .92) except for a borderline significant correlation between abnormality spread score and CRT (p=.061; slope = .478) suggesting a higher abnormality spread score for those who received CRT. White matter abnormalities were present in irradiated as well as non-irradiated patients, but in irradiated patients the abnormalities were more wide-spread and in some cases non-adjacent to the tumor lesion correspondent with the radiation field. (Fig 1 and 2)

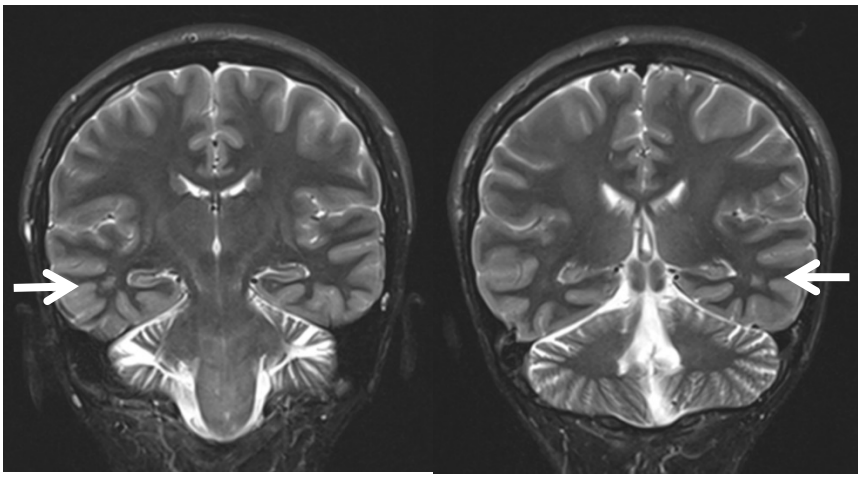

Fig 1.
T2 weighted coronal MR images showing bilateral temporal white matter changes (white arrows) in the irradiation field in a patient with brain stem glioma.

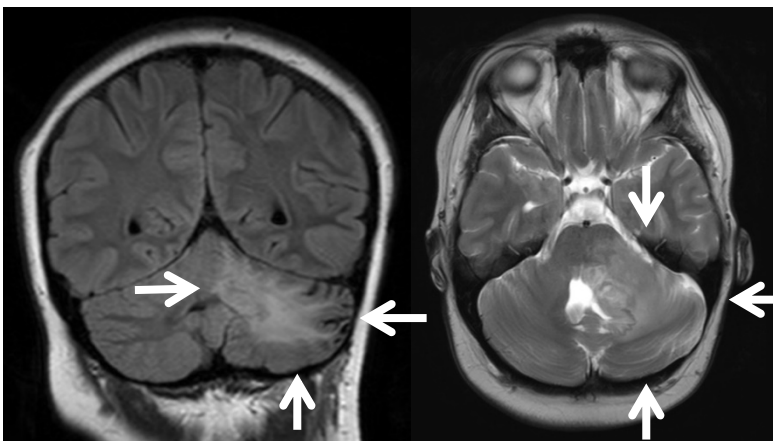

Fig 2.
Fluid attenuated inversion recovery (FLAIR) coronal (a) and T2 weighted axial (b) MR images showing extensive lesional and perilesional parenchymal changes (white arrows) in a non-irradiated patient.

Comparison of Cognitive and Imaging Findings

Analysis 1- Quantitative

MRI abnormality spread scores and neuropsychological data did not correlate on a group level. Bivariate correlations between each one of the 43 neuropsychological measures and the abnormality spread score did not show any significant correlations, p-values ranging from .176 to .949.

Analysis 2 – Personalized Multidisciplinary

Re-evaluation of congruency between cognitive outcome and MRI findings in conjunction with the multidisciplinary personalized assessment yielded congruency in all cases but one (Table 6). The main reasons for changing the initial decision on congruency were: knowledge of premorbid cognitive difficulties (based on clinical anamnesis, early test results and test result patterns), pre-existing or associated diseases such as tuberous sclerosis, MRI findings in eloquent brain areas related to clinical deficits rather than pure size and location, and neuropsychological test results without any impact on adaptive function.

Table 6.
Comparison between the quantitative and personalized methods of comparing cognitive and imaging data.

Pat nr	Quantitative analysis			Personalized approach		
	MR score*	CI †	Congruency	Congruency	Score shifted	Factors contributing to 1/ shift of congruency or 2/ persistent incongruency
1	MR-	CI+	No	Yes	CI	Premorbid difficulties not related to tumor shown in the longitudinal trajectory of the neuropsychological data.
2	MR+	CI+	Yes	Yes		
3	MR+	CI+	Yes	Yes		
4	MR-	CI+	No	Yes	CI	Congruity between MRI and adaptive skills. Limited cognitive impairment in visual memory with less impact on adaptive skills.
5	MRI+	CI+	Yes	Yes		
6	MRI-	CI-	Yes	Yes		
7	MRI+	CI+	Yes	Yes		
8	MRI+	CI+	Yes	Yes		
9	MRI-	CI+	No	No	MR& CI	Cognitive difficulties typical for radiation therapy and low premorbid capacity due to neurofibromatosis 1. No rehabilitation offered.
10	MRI+	CI+	Yes	Yes		
11	MRI+	CI-	No	Yes	MR	Cysts located beyond lesional generates high MR abnormality spread score, but are of no clinical significance and unrelated to the tumor.
12	MRI+	CI+	Yes	Yes		
13	MRI+	CI+	Yes	Yes		
14	MRI-	CI-	Yes	Yes		
15	MRI-	CI+	No	Yes	CI	Premorbid difficulties.
16	MRI+	CI+	Yes	Yes		

* MRI+ assigned to patients with an MRI abnormality spread score ≥ = 3.
† CI: cognitive impairment. CI+ assigned to patients with ≥ 10% of the 43 neuropsychological variables below 1 standard deviation compared to normal.

Discussion

In this study we found that PBT survivors with a varied cognitive outcome 10-13 years after diagnosis have varying degree of brain abnormalities as indicated by MRI. White matter abnormalities were found in patients treated with and without CRT treatment but they seemed to be more widespread in irradiated patients. The correlation between brain abnormalities as indicated by MRI and cognitive functioning and adaptive status as indicated by neuropsychological testing was weak when applying a strictly quantitative approach and improved when a personalized clinical approach was applied.

It could be argued that there should be no strong correlation between MRI and neuropsychological measures since functional and structural measures are not measuring the same thing, e.g. one earlier study showed no correlation between MRI findings and function by the time of diagnosis (Iuvone et al., 2011). However most studies examining white matter abnormalities related to radiation therapy show that such a link exists (Aukema et al., 2009; Brinkman, Reddick, et al., 2012; Jacola et al., 2014; Mabbott et al., 2006; Palmer et al., 2012; Reddick et al., 2014; Spreafico et al., 2008).

Where a link between structural MRI and cognitive function in PBT patient exists, it should be assumed that several complex processes are involved. First, there is complexity in the causes to the brain damage: the tumor itself (Iuvone et al., 2011), hydrocephalus (Aarsen et al., 2009), chemotherapy (Di Pinto et al., 2012), radiation therapy (focal or whole brain)(Merchant, Schreiber, et al., 2014) and neurological complications (Moxon-Emre et al., 2014) all having a negative impact on the brain. Each factor also exerts it specific detrimental effect through different processes in the brain. Even a single pathogenic factor like chemotherapy affects brain cells through several negative mechanisms (Ahles & Saykin, 2007; Saykin, Ahles, & McDonald, 2003) all supposedly giving rise to different structural abnormalities. Second, some studies have shown that genetic susceptibility also plays a role in an individual brain's vulnerability to cancer treatment (Krull et al., 2013). Third, there is the complexity that arises when taking a developmental perspective. A developing brain sustaining an injury will continue to develop along the lines that the damage dictates and then compensates as much as possible for any functional losses. That makes the effect of an injury sustained once (e.g. actual loss of brain parenchyma due to surgery) different from an injury that is thought to permanently change the cell's abilities (e.g. CRT) (Dennis et al., 2013).

Conclusions

Irradiated patients as well as non-irradiated patients show white matter abnormalities beyond the surgical defect caused by removal of the tumor. The understanding of a single patient's cognitive sequelae in the context of PBT may benefit from a clinical personalized evaluation of both structural and functional data obtained from MRI and neuropsychological tests respectively. The relationship between cognitive deficits in PBT patients and data obtained from structural MRI should be viewed as complex and dependent on several factors: initial pathogenesis, genetics, the individual's development and varying vulnerability within the brain.

Study IV. Development After Pediatric Brain Tumor - A Longitudinal Study

Background

Children treated for Pediatric Brain Tumors (PBTs) are at increased risk for declines in cognitive functioning. The most common cognitive sequelae in PBT survivors are difficulties with cognitive tempo, attention, working memory and executive functions (Kahalley, Conklin, et al., 2013). The available longitudinal studies of treated PBT survivors also suggest a significant decline in overall cognitive functioning with Full Scale IQ (FSIQ) drops ranging from 1 to 4.3 Standard Scores (SS) per year (Kieffer-Renaux et al., 2005; Ris et al., 2001). Data from a longitudinal study (Palmer et al., 2001) examining both raw data and standardized from IQ scores in a PBT sample suggest that the cognitive decline may reflect slower development rather than deterioration. When examining cognitive decline in PBT survivors, most studies have fitted linear models to the observed data with a few studies proposing quadratic development model, i.e., a steep decline in IQ immediately following treatment then plateauing over several years (Mabbott et al., 2005; Palmer et al., 2003; Spiegler et al., 2004).

Cognitive decline is mostly seen in patients with medulloblastoma receiving Whole Brain Radiation Therapy (WBRT). Studies examining patients with other types of tumors or patients receiving only focal CRT or reduced dose WBRT have found mixed results. In an early longitudinal study, Ellenberg et al. (1987) found WBRT but no other types of treatment to be related to cognitive decline. Examining attentional abilities among patients receiving focal conformal CRT, Kiehna et al. (2006) found only one out of four different aspects of attention to decline after CRT even if attentional abilities were depressed from baseline. Di Pinto et al. (2010) found stable or improved learning performance after localized conformal radiation therapy and Netson et al. (2012) found stable cognitive performance in ependymoma, craniopharyngeoma and low grade glioma survivors (Netson et al., 2013).

As a contrast two studies have found declining academic abilities in patients with low grade gliomas (Conklin et al., 2008; Merchant et al., 2009). In studies finding a cognitive decline most common risk factors for cognitive decline after PBT are WBRT, young age at diagnosis (Kieffer-Renaux et al., 2005; Knight et al., 2014; Mulhern et al., 2005), hydrocephalus (Moxon-Emre et al., 2014), higher baseline IQ (Palmer et al., 2013; Palmer

et al., 2003; Ris et al., 2001; Ris et al., 2013), and larger radiation field/higher radiation dose (Mabbott et al., 2011; Merchant et al., 2006). Sex differences have been found and most studies have found females to be more vulnerable (Di Pinto et al., 2012; Kiehna et al., 2006; Ris et al., 2001) while others found males to be more vulnerable (Conklin et al., 2008).

Purpose

The aim of this longitudinal study was to study the long term trajectory of the cognitive sequelae and identify risk factor for negative development.

Methods

Patients

Skåne University Hospital supplies cancer treatment to all patients diagnosed with PBT in the south of Sweden. In 2006 a neuropsychological follow-up screening program for all patients diagnosed with PBT was started at Skåne University Hospital in Lund. The goal of the program was to find and offer rehabilitation to patients with cognitive sequelae and to learn more about risk factors and cognitive trajectories. All patients diagnosed with a PBT between 2001 and 2013, who had survived more than one year, were included in the neuropsychological screening program (n=179). In addition patients diagnosed with a PBT between 1993 and 2001 and who turned 18 years of age between 2006 and 2013 were included in the program (n=23).

Neuropsychological testing was done at base-line (i.e. before surgery if possible or directly after surgery when the child had recovered), 1, 3 and 5 years after diagnosis and at 18 years of age before transfer to adult health care. Of the 202 patients eligible for the study, 25 did not undergo neuropsychological screening and were excluded from the present study. One patient was also excluded who had a single evaluation 7 years prior to diagnosis of PBT because of cognitive difficulties related to neurofibromatosis. Three patients were excluded since they were assessed using tests out of their age range (e.g. Bayley Scales of Infant Development (Bayley, 2006) at 10 years of age). This left 173 patients in the study. Retrospective clinical data from the neuropsychological records were also collected to increase the stability of the statistical model and all tests done outside the fixed intervals of the study were included.

Statistical Methods

Multilevel Linear Modelling (MLM) was used to evaluate change over time (growth curves) in cognitive functioning assessed by neuropsychological tests. An overview of all clinical and cognitive variables collected used in the multivariate analyses is given in Table 7. A total of 14 clinical and 12 cognitive variables were examined using MLM. Separate models were built for each of the cognitive variables and both linear and quadratic models were evaluated. The 14 clinical variables were added one at a time in separate models. An unstructured covariance matrix was chosen in order to evaluate both random slopes and random intercepts. A significance level of $p = .05$ was used and no correction was made for multiple analyses.

Cognitive Measures

Measures were chosen to assess areas of cognitive functioning known to be affected in PBT patients (Table 7). Most neuropsychological evaluations were carried out by neuropsychologists working in the Pediatric Neuropsychology Service at Skåne University Hospital using standardized measures. A few evaluations were done at rehabilitation centres using standardized measures.

Table 7.
List of clinical and cognitive variables used in the multivariate analyses, 14 clinical and 12 cognitive variables.

Clinical variables	Comments	Cognitive variables
Sex	Female=0, Male=1	General cognitive ability (FSIQ)
Age at first diagnosis	Years	Verbal ability (VCI)
Tumor size	Largest diameter in cm at diagnosis	Perceptual reasoning (POI)
Astrocytoma	0/1	Auditory working memory (FDI)
Infratentorial tumor	0/1	Cognitive processing speed (PSI)
Supratentorial lateral tumor	0/1	Visual working memory (Block span)
Supratentorial midline tumor	0/1	Verbal learning (Word list), immediate
Increased Intracranial Pressure at diagnosis	0/1	Verbal learning (Word list) delayed
Ventriculoperitoneal shunt or ventriculostomy	0/1	Executive function, flexibility (TMT)
Chemotherapy	0/1	Verbal fluency semantic
Cranial Radiation Therapy, focal	0/1	Verbal fluency phonologic
Whole Brain Radiation Therapy	0/1	Attention sustained visual
Epilepsy	Coded as 1 if seizures occur after the immediate postoperative period	
Relapse within the study period	0/1	

Abbreviations: FSIQ: Full Scale IQ, VCI: Verbal Comprehension Index, POI: Perceptual Organization Index, FDI: Freedom from Distractibility Index, PSI: Processing Speed Index, TMT: Trail Making Test

Results

Four hundred and thirty-three examinations conducted on the 173 patients were analyzed. Most of the patients received between 1 and 4 neuropsychological examinations (involving multiple tests) and were followed over an average of 4.21 years. The average time between examination and diagnosis (pooled over all data-points) was 3.29 years, ranging between -0.59 years and 16.97 years. Ninety-six of the examinations (22.1%) were done at baseline, i.e. within three months of diagnosis, most often before surgery.

Multilevel Linear Models

In the first model built, patients with neurocutaneous syndromes (n=22) showed a distinct profile, differing from the rest of the sample with less treatment. These patients were excluded leaving 151 patients with a total of 387 examinations for the following statistical models.

An overview of all models tested can be found in Table 8. The trajectories of general cognitive ability (FSIQ) and perceptual reasoning (POI) were best described by a quadratic model while all other cognitive variables were best described using linear models. For this PBT sample, the baseline general cognitive ability (FSIQ) was in the average range (99.18 Standard Score (SS)) with a subsequent negative linear trend with a drop of 2.5 SS per year modified by a quadratic trend of increasing IQ with 0.15 SS per squared year since diagnosis. A similar trend was found for perceptual reasoning. The observed linear trajectories for verbal ability, auditory working memory, processing speed and sustained attention all had a negative slope with a yearly drop ranging from 0.49 SS/year (visual working memory) to 1.32 SS/year (verbal ability).

Two cognitive abilities differed in their long term trajectories: Verbal Long Term Memory (word list learning) and Semantic Verbal Fluency. The models describing the trajectory of verbal learning (word list) showed a non-significant positive trend which became significant if age-at-diagnosis was added as a covariate. Semantic verbal fluency was best described by a model with a linear increase of 1.17 SS per year. No model showed a significant variance in slopes related to clinical variables, i.e. all patients regardless of clinical characteristics showed a similar rate of decline (progression) in cognitive functioning. In most models there was significant variance between individuals regarding the estimated baseline value, i.e. cognitive function at diagnosis.

Lower baseline values were correlated with 8 clinical variables: being male, WBRT, young age at diagnosis, supratentorial lateral tumor, larger tumor size, chemotherapy, cranial RT and ventriculoperitoneal shunt. Six clinical variables did not significantly predict cognitive outcome: Midline or infratentorial tumor, astrocytoma, epilepsy, IICP at diagnosis, and relapse.

Table 8.
Summary of all multilevel linear models. Statistics for significant models are shown in table 5 a-i. For all models an unstructured covariance matrices was used.

Test	N	Data-points	Type of change over time	Variables adding significant explained variance to the model
General cognitive ability (FSIQ)	150	364	Negative linear slope modified by quadratic positive slope	Sex
Verbal ability (VCI)	146	366	Negative linear slope	Supratentorial lateral tumor
Perceptual reasoning (POI)	146	359	Negative linear slope modified by quadratic positive slope	WBRT
Auditory working memory (FDI)	142	340	Negative linear slope	Sex, supratentorial lateral tumor, WBRT
Processing Speed (PSI)	140	340	Negative linear slope	Sex, tumor size, CRT, VP shunt
Visual working memory (block span)	118	224	No significant change over time.	Significant change over time, only with chemotherapy as covariate, negative linear change.
Verbal learning immediate (Word list)	140	307	No significant change over time.	Significant change over time, only with age as covariate, **positive** linear change.
Verbal learning delayed (Word list)	118	236	-	Convergence was not reached
Executive function (TMT)	113	217	-	Convergence was not reached
Verbal fluency semantic	135	294	**Positive** linear slope	Sex, age at diagnosis, tumor size
Verbal fluency phonologic	122	246	-	Convergence was not reached
Attention sustained	131	272	Negative linear slope	Convergence was not reached for any covariate added

Abbreviations: FSIQ:Full Scale IQ, VCI: Verbal Comprehension Index, POI: Perceptual Organization Index, FDI: Freedom from Distractibility Index, PSI: Processing Speed Index, TMT: Trail Making Test, WBRT: Whole Brain Radiation Therapy, CRT: Cranial Radiation Therapy, VP: VentriculoPeriotonea

Discussion

The general decline in IQ is consistent with several earlier studies examining medulloblastoma survivors (Palmer et al., 2013; Schreiber et al., 2014) as is the finding of quadratic and linear declines depending upon the particular aspect of cognitive functioning assessed (Knight et al., 2014; Palmer et al., 2003). We could not replicate the finding of stable cognitive performance in children not treated with WBRT (Copeland, deMoor, Moore, & Ater, 1999; Netson et al., 2012) since all statistical models showed a general cognitive decline across patient and treatment categories. Few longitudinal studies on cognitive performance after PBT treated without chemotherapy or CRT have been done with one exception being a study by Fouladi et al. (2005). In that study the authors identified a sub-group of 37 PBT survivors treated with surgery alone from their sample of 194 survivors who had been diagnosed before three years of age. Fouladi et al. (2005) found improved cognitive performance over time for survivors treated with surgery alone or surgery plus chemotherapy, while in the present study the opposite was found. Some cross-sectional studies however found cognitive impairment in PBT survivors treated with surgery alone (Aarsen, Van Dongen, Catsman-Berrevoets, Paquier, & Van Mourik, 2004; Beebe et al., 2005; Ris et al., 2008) but this group of patients remains understudied.

Two verbal abilities in this study were shown to have a positive or stable trajectory: semantic verbal fluency and word list learning. The latter is in line with two previous studies by Spiegler et al. (2004) and Di Pinto et al. (2012) who noted a stable performance on word list learning. It is important to note that others have found the opposite, i.e., declining/negative trajectory for word list memory (Kieffer-Renaux et al., 2000; Robinson et al., 2013).

Consistency in Cognitive Trajectories and Variance in Baseline Measures

No clinical variable predicted the rate of cognitive decline after PBT which was unexpected since earlier studies have found several factors to determine the rate of decline, e.g. hydrocephalus and age at diagnosis (Mabbott et al., 2005; Mulhern et al., 2005). Eight of the 14 clinical factors predicted the estimated baseline, i.e. cognitive ability at diagnosis. This implies that pre-treatment risk factors play a larger role than treatment in predicting long term cognitive sequelae. The fact that treatment factors, primarily WBRT but also focal CRT and chemotherapy, predicted cognitive ability at diagnosis was unexpected since treatment is given later. It might be a result of limitations of the statistical models and the heterogenic sample (i.e. only linear and quadratic models could be modelled). However this observation is partly in line with a previous study by Di Rocco et al. (2010) who examined 41 patients with posterior fossa tumors, 18 of them with medulloblastomas and the rest of them with pilocytic astrocytomas. The authors found that patients with medulloblastomas

were more likely to have impaired cognitive performance both pre- and post-surgery (before any other treatment was given).

Considering the multifactorial origin of cognitive sequelae in PBT patients it is likely that the trajectory of cognitive sequelae is very individual and not easily described by a single statistical function like slope (i.e., trajectory of neurocognitive functioning over time). For example, Stargatt et al. (2007) propose different trajectories of cognitive development after PBT with one timeline for tumor/surgery related injury (worsening first year, then stable) and one timeline for chemotherapy and CRT related injury (later decline). If this holds true, two medulloblastoma patients treated with the same treatment could have totally different cognitive trajectories depending on whether they suffer more or less from sequelae related to hydrocephalus, surgery or WBRT. Studies with a more personalized approach are needed to better describe the multifaceted cognitive trajectories that can occur after PBTs.

Sex

Male sex was one of the most influential predictors of impaired cognitive performance at baseline which is in contrast to most earlier longitudinal studies showing female sex to be related to steeper cognitive decline after PBT treated with CRT (Di Pinto et al., 2012; Merchant, Schreiber, et al., 2014; Netson et al., 2013). We have earlier showed male gender to be related to larger tumors at diagnosis, given that the initial symptom is hydrocephalus (Tonning Olsson, Perrin, Lundgren, Hjorth, & Johanson, 2014), however in this sample the gender differences cannot be explained by males having larger tumors since no such (significant) relation was found. Since no earlier longitudinal study have examined gender and cognitive trajectory in patients treated with surgery alone a proposed theory might be that girls are more vulnerable to cognitive sequelae after PBT treatment with chemotherapy or radiation, while males are more vulnerable to cognitive sequelae related to the tumor itself, surgery and hydrocephalus.

Conclusions

Pediatric Brain Tumor survivors show declining cognitive skills regardless of treatment type except for elementary verbal skills which appeared to be stable or improving. Male sex, treatment with WBRT, supratentorial (lateral) tumors, young age-at-diagnosis, larger tumor size and treatment with chemotherapy were the main predictors of lower baseline cognitive performance. Cognitive measures at diagnosis could be used to identify patients at risk for later cognitive sequelae but more longitudinal studies are needed with PBT survivors are needed with large sample sizes so that they include patients not treated with chemotherapy or CRT.

Discussion

Findings from the Four Studies

Overall, the four studies descried here add to previous research demonstrating an increased risk of long-term cognitive impairments in PBT survivors and thereby underlining the importance of systematic and repeated neuropsychological assessments as part of the long-term care of PBT survivors. We replicate previous findings showing that younger age-at-diagnosis and tumor size are significant risk factors for late cognitive sequelae, and in contrast with previous studies suggesting that girls are at greater risk of cognitive impairment, we found boys to be at greater risk. Further we have addressed the complex relationship between neuro-imaging and neuropsychological findings, showing that a personalized multi-professional approach is needed to interpret and correlate these two important sources of data. In our longitudinal study we confirmed earlier findings of a decline in IQ over time for PBT patients, uniform over patient categories.

Factors Correlated with Cognitive Sequelae.

The main focus of the present research program was to examine clinical and demographic risk factors for cognitive sequelae in PBT survivors. The current research program benefitted from a large sample size drawn from a specialist pediatric clinic serving the southern part of Sweden, the use of standardized measures of IQ and other indices of cognitive functioning in a longitudinal fashion. While there have now been a relatively large number of studies investigating such risk factors, the frequent use of small samples, the lack of longitudinal designs, a sufficiently broad array of neuropsychological measures, and lack of specificity in the assessment of risk relationships has limited the conclusions that can be drawn. For example several studies have shown CRT to be a risk factor for cognitive sequelae without differentiating between focal RT and WBRT, a distinction which has shown to be crucial in many studies including our own (Fuss et al., 2000; Tonning Olsson et al., 2014). Nevertheless, studies using multiple regression models, including our second study, have found clinical and demographic variables to explain between 15% and 48% of the variance in the cognitive outcomes, suggesting additional risk factors are involved in the development of long-term cognitive deficits in PBT survivors (Aarsen et al., 2009; Reimers et al., 2003; Tonning Olsson et al., 2014). Several such factors have been

identified in the literature but for various reasons were not measured here, including but not limited to: genetic vulnerability, socio-economic status, pedagogic environment, cognitive/behavioral rehabilitation, individual and family coping styles/resources, and psychological well-being (Grill et al., 1999; Krull et al., 2013; Patel et al., 2015).

Sex Differences

Sex differences in the incidence and survival from PBTs are found in the literature. More males than females are diagnosed with PBTs (sex ratio = 1.11 to 1) (Lannering et al., 2009). The overall survival rate from PBTs does not differ between males and females, however the incidence of medulloblastoma is higher in males and males have lower survival rates for this commonly occurring type of PBT (Curran, Sainani, Le, Propp, & Fisher, 2009; Lannering et al., 2009). So when considering gender differences in cognitive outcomes from PBT it is important to keep in mind that any observed differences may be partly related to how incidence and survival affects the make-up of studied samples.

In our studies we have found male sex to be associated with lower baseline cognitive functioning and to act as a risk factor for later cognitive impairment. Earlier research results on sex and cognition after PBT yield diverse findings with the most recent longitudinal studies reporting a vulnerability (for females, not males as found here) being based on samples of children with medulloblastomas. Thus the contrast between the present and previous findings may be owing to the heterogeneity of cancer types in the current sample. Setting aside cancer subtypes, female vulnerability to cognitive impairments has been most consistently reported in patients treated with chemotherapy and/or RT. The current findings add to the literature and the differences found here may arise from the fact that half of the sample had surgery only (in comparison to previous studies).

In one of our studies we have found males to have larger tumors at diagnosis given that the initial symptom is IICP, presumably because of wider male head circumference, allowing the tumor to grow larger before symptom onset. Larger tumors were in turn correlated with worse cognitive outcome. Since no studies have shown initial tumor size to predict worse cognitive performance before treatment (Brookshire et al., 1990; Iuvone et al., 2011) this correlation is probably secondary to factors like larger radiation field, more complicated surgery and IICP.

G. T. Armstrong et al. (2007) have pointed out the need for verifiable theories that try and posit specific biological mechanisms that might explain any observed gender differences in cognitive functioning after PBTs. They argue that hormonal differences are not a plausible candidate for a theory because hormonal differences between pre-pubertal boys and girls are quite small. They offer as a suggestion that gender differences in the rate of DNA-repair might explain differences in response to cancer treatments but acknowledge that no studies have yet evaluated this possibility. Another explanation might be that sex differences in rates of white matter maturation might interact with damage to the brain caused by cancer

treatment but again this remains uninvestigated (Jacola et al., 2014; Koolschijn & Crone, 2013). This last hypothesis might explain why sex differences are more prominent in survivors of Acute Lymphoblastic Leukemia (ALL). ALL is usually diagnosed within a quite limited age-span, which is not the case for PBTs, and girls might be in a more vulnerable brain maturation phase during the age-span when ALL is diagnosed. Clearly more research is needed to understand gender-specific risk factors and how these interact with tumor size, incidence and survival rates.

Systematic Neuropsychological Follow-Ups

Investigators carrying out research on cognitive sequelae in PBT survivors have reached the same conclusion, i.e. that systematic and standardized neuropsychological follow-ups are essential to both the patient and to the further development of this field. As regards the patients' needs, ours and other studies have shown that different types of cancer treatments bring with them different risks of cognitive decline. Such information needs to be shared with families and to be weighed against the risk of mortality when choosing among different evidence-based treatments. Our research and other studies show that in the aftermath of diagnosis and treatment, many PBT survivors have significant and subtle cognitive impairments that go undetected for long periods and thus appropriate supports may not be offered (Hoven et al., 2011; Kahalley, Wilson, et al., 2013; Tonning Olsson, Perrin, Lundgren, Hjorth, & Johanson, 2013). The long-term pattern of cognitive decline for a significant proportion of PBT patients observed here and in other studies (Merchant, Schreiber, et al., 2014; Moxon-Emre et al., 2014) strongly suggests that neuropsychological follow-ups be continued throughout childhood and into adulthood. Such systematic and repeated neuropsychological evaluation may lead to significant improvements in adjustment during childhood and adulthood if data from the assessments are communicated to the family of the survivor and to the appropriate health professionals, assuming the relevant supports are implemented and effective. Recognizing these potential benefits, guidelines for clinical follow-up are now published by the North American Children's Oncology Group (COG) (Nathan et al., 2007). COG recommends all childhood cancer survivors at risk for neurocognitive impairment, to have at least one neuropsychological evaluation at baseline when entering a long-term follow-up program. Assessment is also recommended for all survivors when school difficulties are experienced for the first time, followed by assessment at appropriate intervals considered the survivor's specific medical and developmental risk factors and/or at transition to new schools. Research guidelines have been published by the International Society of Paediatric Oncology Europe (SIOP-E) (Limond et al., 2015) and by COG (Noll et al., 2013). The SIOP-E guidelines do not specify time-points for assessment but refers two studies with assessment points between neurosurgery and treatment, 24 and 60 months from diagnosis and at 18 years of age for the first study and 9, 30 and 60 months from diagnosis for the second study (ALTE07C1)(Embry et al., 2012). All three sets of guidelines recommend

approximately the same cognitive areas to be assessed; verbal and non-verbal general cognitive ability, memory, attention, executive function and cognitive processing speed.

The implementation of systematic neuropsychological assessments in the aftermath of PBTs are also essential to scientific advances in our understanding of the 'effectiveness' of different cancer treatments as well as moderator and mediators of longer-term outcomes including cognitive and psychosocial adjustment. Great amounts of money and effort are put into modifying cancer treatment protocols to reduce negative cognitive sequelae and the effects of those efforts need to be evaluated. Data from repeated, standardized neuropsychological assessments must be pooled across treatment center and countries because PBTs are a relatively rare disorder with great heterogeneity in terms of type, locality, and age at onset etc. Even regional and national treatment centers like the one sampled from here may have relatively few patients with rare subtypes of tumors who received a certain treatment and with a particular baseline clinical picture.

While there is now international consensus in the value of neuropsychological follow ups, implementation has and will prove difficult. In in their study evaluating a brief neuropsychological assessment battery, Embry et al. (2012) identified several factors impeding implementation: 1) reliance upon lengthy assessment batteries requiring considerable skill, time and cost to administer and score; 2) reliance upon tests that are not widely available to all practitioners; 3) limited access to adequately trained pediatric neuropsychologists; and 4) the absence (or limitation) of electronic systems for monitoring and sharing data (e.g. local, regional, national and international PBT registries).

Several attempts have been made to develop shorter test batteries tackling the first two obstacles, e.g. by Limond et al. (2015), Embry et al. (2012), and Ottensmeier et al. (2014). All of these batteries take around 1 hour to administer and can pinpoint functional areas known to be impaired in PBT survivors. Krull, Okcu, et al. (2008) have developed a test battery requiring only 30 minutes designed to be used for all pediatric cancer patients. The same group has also developed a neurocognitive questionnaire to assess cognitive impairments in adult PBT survivors (Krull, Gioia, et al., 2008). Another way to simplify the assessment is to use computerized assessment as have been done by Conklin et al. (2013). They examined the feasibility of a computerized test battery "Immediate Post-Concussion Assessment and Cognitive Testing" (ImPACT), primarily developed for monitoring recovery in individuals sustaining mild brain injuries, and found it useful for PBT survivors as well. Overall, it is extremely important to develop and implement systematic neuropsychological screening using valid and cost effective methods.

Understanding the Biological Background

Several authors have pointed out the need to understand the biological causes to the cognitive sequelae and thereby possibly preventing them. This is suggested to be achieved through several different approaches, such as linking functional and structural

neuroimaging data to cognitive data (Brinkman, Reddick, et al., 2012; Palmer et al., 2012), understanding the basic cellular mechanisms (Ahles & Saykin, 2007; Kalm et al., 2009; Saykin et al., 2003), identifying genes connected to vulnerability (Brinkman, Reddick, et al., 2012; Krull et al., 2013) or studying risk factors in detail, e.g. different doses of CRT given to different parts of the brain (G. T. Armstrong et al., 2010; Merchant et al., 2006; Ris, 2007). Ahles and Saykin (2007) reviewed cellular mechanisms behind cognitive sequelae after chemotherapy treatment in adults and concluded several mechanisms are involved and interacting. Simple correlations between treatment, neuroimaging and cognition are therefore not expected to be found.

The focus in studies examining the biological basis of cognitive sequelae has largely been on white matter damage, mostly in radiated patients (Jacola et al., 2014; Reddick et al., 2014) but also in non-radiated patients (Rueckriegel et al., 2010). White matter consists of dendrites and axons, i.e. connections between cell bodies. Since the brain is a neural network, a disruption in neuronal connections between brain regions might be expected to cause overarching global impairments rather than specific focal deficits. PBT patients have deficits in processing speed, working memory, attention and executive function, all general overarching abilities depending on well-functioning networks between brain regions (Brinkman, Reddick, et al., 2012).

Some authors have stressed the role of damage to cerebello-thalamo-cortical tracts in cognitive sequelae after PBT, either direct damage caused by surgery and/or CRT or via diaschisis. This has been studied in patients with Cerebellar Mutism Syndrome (CMS) and in radiated patients. Miller et al. (2010) examined cerebral blood flow in eleven patients with CMS showing reduced frontal blood flow and Law et al. (2011) showed damage to cerebellar-thalamo-cortical tracts in radiated patients related to working memory deficits. Cantelmi et al. (2008) reviewed the evidence for the role of cerebellum for cognitive sequelae after PBT and state:

> "These studies have shown that the cerebellum is a contributing node in an extensive corticosubcortical network. Efferent fibres leave the cerebellar nuclei and reach the cerebral cortex via thalamic projections, fibres from these same cortical areas then return to the cerebellar cortex via pontine nuclei, establishing a series of closed-loop circuits. Some of the non-motor targets of these closed-loop circuits include the prefrontal cortex, the temporal lobe, and limbic structures." (p570, references left out)

> "… neurocognitive sequelae noted in patients with tumours of the posterior fossa is not due solely to the effects of radiotherapy on supratentorial structures, but rather, in a large part, due to the disruption of key cerebellar circuits, caused by several factors, including, but not limited to, radiotherapy. (p575)

Since half of the PBT patients have tumors in the posterior fossa region, this notion has to be taken into account in further studies examining the relationship between cognition and neuroimaging in PBT survivors. In summary; the relation between cognitive sequelae after PBT and neuroimaging is extremely complex and the research in this field is in its infancy.

Several factors have to be taken into account besides treatment with CRT, e.g. cerebellar damage.

Limitations

The studies described here are based upon data drawn over many years (both retrospectively and prospectively) from a clinic responsible for treating all pediatric cases of PBT in a region of 1.2 million people. No control groups were included. As such, and consistent with most population-based longitudinal studies, the current sample is heterogeneous and experienced changes in treatment strategies along with the neuropsychological tests used to measure cognitive functioning. This together with the absence of control groups limits analysis of particular sub-groups and particular risk relationships. As discussed above, large longitudinal, multicentre studies are needed with systematically coded neuropsychological and medical data and which include the appropriate healthy controls (e.g., siblings of the PBT survivors) as was done in the Childhood Cancer Survivor Study being carried out in the USA (Prasad et al., 2015; Robinson et al., 2010).

In study II and IV we used overarching large statistical models examining variances and covariances (multiple linear regression models, uni- and multilevel). Advantages with this type of analysis is the objective analysis of large trends in data, reduced risk of mass-significance and the possibility to find general trends in large data bases. The disadvantages are the loss of patient specific data and lack of possibilities to include the researcher's clinical knowledge, the risk of extreme values distorting the models and true correlations eliciting each other due to covariance between variables. Therefore results from large statistical models need to be interpreted with caution and supplemented with alternative analysis methods (e.g. more qualitative personalized methods or case studies).

Most studies, including ours, have used IQ indices measured by an age appropriate Wechsler test as the outcome variable. This might not be optimal since IQ, and especially FSIQ is a conglomerate of several different abilities. Furthermore the Wechsler tests are not sensitive to deficits in attention, memory and executive function, three of four core areas of impairment for PBT survivors. For example Carpentieri et al. (2003) found IQ to be within normal limits in a sample of 103 PBT survivors but found impairment in verbal memory and visuospatial organization. Waber et al. (2006) found significant memory deficits but normal IQ in a small sample of craniopharyngeoma patients. It is also a limitation of the Wechsler tests that the subtests for processing speed require fine motor coordination which is often impaired in patients with tumors in the posterior fossa. Still, considering the benefits of implementing a program of systematic neuropsychological assessment for PBT patients, , the Wechsler tests have excellent psychometric qualities and are available in many different languages, are continuously updated and considered the gold standard for intellectual assessment (Grill, Kieffer, & Kalifa, 2004; Ris et al., 2013). To conclude, the Wechsler IQ indices are important measure of cognitive late sequelae after PBT but need to be completed with measures of attention, memory, speed and executive function.

Moving Forward; Clinical Implications and Suggestions for Future Research

Implications for Clinical Practice

Some advice for clinical practice within the field of pediatric neuropsychology and brain tumors has been mentioned above and are summarized again for convenience.

There is now widespread agreement that the most important thing is to insure that all PBT survivors are **systematically followed-up with standardized neuropsychological examinations.** These follow-up screenings may be stratified with full neuropsychological assessments involving multiple tests allocated to patients that need them most. It is important to remember that some PBT survivors do really well cognitively and do not need to spend long hours completing neuropsychological tests but rather a fairly brief screening to make sure they receive adequate levels of support. If resources are very scarce, the neuropsychological follow-ups may be a shorter test-battery supplemented with interview and questionnaire as long as some systematic screening is done (Krull, Gioia, et al., 2008; Krull, Okcu, et al., 2008; Lai et al., 2014; Ottensmeier et al., 2014). Taking account of children's natural development, it is seldom possible to use the same test instruments over the years but similar measures could be used (e.g. Nepsy sentence repetition for younger children and Wechsler digit span for older children to measure auditory working memory (Korkman, 2000; Wechsler, 2007)).

Again the need for systematic neuropsychological screening imposes burdens on both clinical services and the patients. Embry et al. (2012) list several impediments to implementation of a systematic screening, among them lengthy test batteries and tests that are not readily available. As such one approach would be to focus the neuropsychological examination on abilities known to be impaired in PBT survivors, i.e. **cognitive tempo, attention, memory and executive function**. The difficulty will always be to strike the right balance between making the neuropsychological follow-up as **simple and brief** as possible without losing valuable information.

For both clinical practice and research it is important to **cooperate** between cancer centers and countries. Given the heterogeneity among PBT patients, it is necessary to share data, knowledge and experiences with colleagues within the field. In order to implement

multicenter follow-up protocols it is important to **disseminate existing guidelines** and establish some sort of **feedback to the examiners**.

Even if we today are aware of several risk factors for cognitive sequelae, it is not possible to perfectly predict which patients will suffer cognitive impairments, when those impairments may arise, or exactly what type of impairment they may experience. It is equally not possible to predict how an individual's cognitive impairment will affect the interaction between a given setting (family/school) and the child. Thus neuropsychological care needs to be **personalized to the needs of the individualized child**. As Rey-Casserly and Meadows (2008) put it:

> "Specific constraints on development that arise from the disease and/or its treatment in turn become part of the developmental course and can thus have increasing impact over time as specific developmental stages ad contexts demand mastery of more complex tasks and behaviors, and the biological lesion itself may or may not remain static. Within such a model, the goal of management is not only to remediate deficits but also to monitor the potential disequilibrium between the child and environmental demands, and to intervene in ways that can reduce this equilibrium." (p244)

An excellent example of such an individualized approach is given in a case study by Callu et al. (2008) who followed a child treated for medulloblastoma over 11 years and offered the rehabilitation needed at each stage of development. All rehabilitation interventions were defined by a team consisting of the child's teachers, the rehabilitation educators, the child's parents and a person from the hospital team. This team met yearly and evaluated the interventions given. Example of interventions given over the years were: intense language therapy, the use of verbal cues to compensate for poor visuospatial skills, teaching in a small group by a pedagogue specialized in learning difficulties, physiotherapy and psychotherapy.

Suggestions for Future Research

In this section suggestions for future research are summarized, most of them discussed above. Two areas suggested for future research but not included in this thesis, interventions and social ability, are discussed here in more detail.

While it might seem that a lot is already known about risk factors for cognitive sequelae it is still necessary to **expand on, update and research risk factors**. A more strict **quasi-experimental methodology** is needed in this area with more homogenous groups and directional hypotheses, e.g. studies like the one done by Merchant, Schreiber, et al. (2014) holding as many variables as possible constant and varying radiation dose and localization.

Gender differences need to be explored further, including finding and testing theories of why those differences exist.

The **biological background** to cognitive sequelae needs to be better understood. Since causal relationships are searched for, this is probably best done in animal and cell studies, however clinical quasi-experimental studies are also needed.

More studies focused on cognitive ability after **low grade tumors**, treated with **surgery alone** are needed.

Along with a need for more quasi-experimental studies goes a need for studies applying a **more personalized methodology**, comparing each individual's history of disease and cognitive ability and development. Considering the heterogeneity among patients, group based statistics and models describing large trends in data are of limited value.

Studies examining more in detail what **type of cognitive sequelae** PBT survivors suffer from are needed, including studies on the trajectory of different cognitive abilities.

More **longitudinal long-term follow-up studies** are needed.

Models for **cost effective and viable neuropsychological follow-up** for all cancer patients need to be developed and evaluated.

Switching the perspective from what research can do for PBT patients to what studies of PBT patients can provide for neuropsychological research, PBT patients constitutes a very well suited group to **study the function of cerebellum**. Today, we have just begun to understand the role of cerebellum for cognitive abilities and more research is needed (Cantelmi et al., 2008).

As for clinical practice, **cooperation** between professions, health care units and countries is crucial for the development of the field. Without multi-center studies it is not possible to gather large enough homogenous patient groups. Several professions have to cooperate to be able to state directed hypothesis, since this requires knowledge in many different areas, e.g. oncology, neuroradiology, radiation oncology and neuropsychology.

Interventions to Reduce the Impact of Negative Cognitive Sequelae

The best way to handle negative cognitive sequelae is to prevent them from ever occurring, i.e. to alter cancer treatment methods to reduce their risk of cognitive sequelae. When this is not possible the next step is to provide the patient access to evidence-based interventions that facilitate coping with any sequelae or can improve cognitive functioning. Studies have been done showing positive results from stimulant medication in PBT survivors (Conklin et al., 2007; Conklin et al., 2010; Mulhern, Khan, et al., 2004). Several types of non-pharmacological rehabilitation have been described and some have begun to be evaluated: therapeutic interventions, adaptation of the child's environment, training of specific skills, and overarching holistic rehabilitation models.

Therapeutic Interventions

The neuropsychological evaluation has a two-fold goal: to map cognitive strengths and weaknesses and to change the knowledge and understanding of the difficulties, within the child and the people surrounding her/him. In this aspect the evaluation is an intervention in itself, helping the child and family to cope with the impairment. This aspect of the evaluation has been enhanced and elaborated in "Therapeutic Assessment", a method where tests are used as therapeutic tools and the patients and her/his parents are seen as a co-explorers of problems presented (Finn & Martin, 2013). This approach has not been used for PBT patients, even if elements of it are used in most clinical neuropsychological evaluations.

Pure therapeutic interventions might also be needed for PBT patients and their families. Parents might need help to mourn their child's lost abilities to be able to put reasonable demands, older children/teenagers might need psychological techniques to cope with stress or families might need help to redefine roles.

Adaptation of Environment

The most common intervention is probably adaptation of the environment, such as school curriculum modification, learning aids, adapted teaching materials etcetera. The clinical neuropsychological evaluation is often summarized in a report with suggested interventions, which might help teachers and parents to find ways to adapt the home and educational setting. It is of importance that this report is communicated in a clear way to patients, family and teachers for the interventions to be implemented (Cheung et al., 2014). Several large cancer centers have developed school liaison programs to accomplish this (Rey-Casserly & Meadows, 2008). Even if more research is needed to confirm the effectiveness of such programs, some evidence exists and such programs are appreciated and requested by parents and teachers (Bruce, Newcombe, & Chapman, 2012). More research is also needed to establish key elements of such programs. A detailed description of this type of intervention is given in a case study by Callu et al. (2008).

Training of Specific Skills

Training interventions designed to improve specific skills have been developed for attention, executive function, working memory and general cognitive ability (Hardy et al., 2012; Kesler, Lacayo, & Jo, 2011; Patel, Katz, Richardson, Rimmer, & Kilian, 2009; van't Hooft & Norberg, 2010; van 't Hooft et al., 2007). Most of those training programs involve the patient as well as his/her family and school. The studies show positive effects but the importance of offering this intervention to the right group of patients is pointed out by the authors. Several studies have shown that survivors of PBT have impaired physical ability and are more often physically inactive (Florin et al., 2007; Ness et al., 2010; Piscione, Bouffet, Mabbott, Shams, & Kulkarni, 2014; Rodgers, Trevino, Zawaski, Gaber, & Leasure, 2013) and programs aimed at increasing physical activity and thereby improve cognition have been started (Cunningham et al., 2012; Rodgers et al., 2013).

Holistic Rehabilitation

The holistic approach to brain injury rehabilitation have been developed and evidenced in several studies (Marcantuono & Prigatano, 2008). This paradigm is characterized by a view of the brain-injured individual as an active and unique participant in the rehabilitation process rather than a passive receiver of services. The therapeutic element of the rehabilitation process in emphasized in this perspective and the goal is to help the individual to process, overcome, accept and cope with the disabilities she/he has got. Such rehabilitation programs are developed in a therapeutic environment and the patient/pupil has a named coach/therapist and the relation to her/him is considered crucial. Fletcher-Janzen and Kade (in Marcantuono & Prigatano, 2008) developed a 6-step goal model for rehabilitation of brain injured children within the holistic perspective. The six steps are:

> "…1) engagement in the rehabilitation process, 2) awareness of deficitis, 3) mastery of compensatory strategies, 4) control, 5) acceptance of personal deficits and the ability to incorporate necessary changes in their life while 6) forming a sense of identity for the child." (p.458)

Within this approach Butler and Copeland (2002) developed a rehabilitation program for PBT and ALL patients suffering from cognitive sequelae, called the Cognitive Remediation Program (CRP). In CRP methods from three different disciplines are combined:

1. From brain injury rehabilitation: Methods for training of specific skills e.g. attention (see section above).
2. From education discipline: Techniques and strategies to teach metacognitive skills.
3. From clinical psychology: cognitive and behavioral interventions aimed to learn the child to be her/his own coach and start and keep an inner dialogue to guide her/his behavior and learning.

This program was evaluated in a pilot study and in a subsequent multi-center trial (Butler & Copeland, 2002; Butler et al., 2008) with mixed results. Participants in both studies were pediatric cancer survivors with a documented attention deficit. The samples were mixed with primarily PBT and ALL survivors and a few patients with other types of cancer having received treatment affecting CNS. The pilot study included 31 cancer survivors, half of them with brain tumors and the multi-center trial included 161 patients. One third of the patients in each study served as a control group. In the first study participants, but not control group subjects, showed improvement on attentional measures. In the second study, improvement was found on academic achievement and parent-reported attention skills, but no significant improvement was found for neuro-cognitive measures. The authors conclude that CRP has shown potential to rehabilitate PBT patients, but further research is needed and attention has to be paid to selecting the right patients/families for the intervention.

The holistic perspective of brain injury rehabilitation offers an attractive alternative to more reductionist views; instead of *giving* the patient the training she/he needs, different activities

are explored together with the patient to find meaningful and feasible training methods. However models applying this perspective are often costly, lengthy and demanding, with high drop-out rates that argue against their effectiveness (Hardy et al., 2012; Kesler et al., 2011). Further research is needed as well as efforts to evaluate the usefulness of the holistic perspective as an overarching theory to guide routine care (e.g. allowing a child longer time on tests) versus formal approaches like CRP.

Social Ability

In focus groups with health care providers and caregivers of medulloblastoma survivors, caregivers rated social functioning to be the most important factor impacting quality of life (Henrich et al., 2014). Many studies report that PBT survivors have impaired social skills, and are less likely to live independently or have a partner, and are more often unemployed (Barrera, Shaw, Speechley, Maunsell, & Pogany, 2005; Hornquist, Rickardsson, Lannering, Gustafsson, & Boman, 2014; Mostow, Byrne, Connelly, & Mulvihill, 1991). Impairment in social skills has been linked to treatment with CRT and or chemotherapy, younger age at diagnosis, posterior fossa syndrome and longer time since treatment (G. T. Armstrong et al., 2010; Wolfe-Christensen, Mullins, Scott, & McNall-Knapp, 2007), i.e. risk factors quite similar to variables predicting cognitive impairment which makes it reasonable to expect a link between cognition and social skills (Gurney et al., 2009). Bonner et al. (2008) found social functioning to be correlated with impaired face recognition and Holmquist and Scott (2002) linked overall cognitive function, verbal memory and learning deficits to social withdrawal and functioning. In a longitudinal study, Brinkman, Palmer, et al. (2012) found a correlation between general intelligence and social improvement/decline and suggested higher intelligence to be a factor of resiliency. Overall it seems like there is a close link between cognition and social competence but more research is needed to understand this link (Fiona Schulte & Barrera, 2010; Yeates et al., 2007).

Often PBT survivors suffer from physical disfigurements, e.g. craniopharyngeoma survivors who are at risk for obesity and strabismus. Mulhern, Carpentieri, Shema, Stone, and Fairclough (1993) found disfigurement to be one of several predictors of social and behavioral problems. At least two studies have evaluated interventions for social functioning (Barakat et al., 2003; F. Schulte, Bartels, & Barrera, 2014) both using a group training program. Both studies showed positive results but more research remains to be done within the area.

Overall social competence is an extremely important area to be researched in the future since it affects many PBT survivors and have devastating effects on quality of survival.

Some Final Words

The research area of cognitive development after PBT has been growing very fast recently, but is still in its infancy. Many studies are yet undone and we have only just begun to understand the need of rehabilitation in our patients and how to offer optimal help. The research within the field of pediatric cancer have been very successful during the last decennia in terms of increasing survival rates, but now is the time to also look at quality of survival, i.e. to look beyond survival.

So – at last – after more than 80 pages describing difficulties and problems and difficulties – it should also be said that some PBT survivors manage quite well in life considering the severe disease they have gone through. Many studies have found IQs and behavioral ratings within normal limits and individual patients with well-preserved cognitive competence (Beebe et al., 2005; Copeland et al., 1999). In our second and fourth study 12% of the patients and 10% of the examinations yielded FSIQs above 115, i.e. one standard deviation above norm mean. Even if this is below the number expected in a general population we need to acknowledge that these survivors exist, many of whom live normal and satisfying lives.

Bortom överlevnad – kognition efter hjärntumör i barndomen

(Summary in Swedish / Svensk sammanfattning)

Bakgrund

Hjärntumör hos barn är en relativt ovanlig sjukdom som drabbar cirka 70 barn i Sverige årligen. Under de senaste 40 åren har överlevnaden i barnhjärntumör ökat avsevärt från under 40 % till över 70 %. Överlevnaden har inte varit utan pris och många barn får kognitiva svårigheter efter behandlingen, t.ex. problem med långsamhet, dåligt minne, bristande uppmärksamhet och bristande exekutiva svårigheter. Detta har skapat en ny grupp patienter i behov av stöd och rehabilitering och det är denna grupps behov som ligger till grund för denna avhandlings fyra studier.

Gruppen barn/unga vuxna som överlevt en hjärntumör i barndomen är inte en homogen grupp och spektret löper från dem som får en grav intellektuell funktionsnedsättning (mental retardation) till dem som inte har några kognitiva svårigheter alls. Vilka och hur mycket svårigheter man får beror på flera olika faktorer: Tumörens typ, storlek och lokalisation, perioder av högt intrakraniellt tryck, operationskomplikationer, vilken behandling som ges och vilka andra komplikationer man får efter behandlingen, t.ex. epilepsi eller hormonbortfall. Faktorer hos det enskilda barnet spelar också in, framför allt har man funnit att låg ålder vid diagnos är en riskfaktor för kognitiva svårigheter. Cirka 10 % av dem som får hjärntumör i barndomen har ett s.k. neurokutant syndrom t.ex. neurofibromatos eller tuberös skleros. Dessa genetiska syndrom orsakar förändringar i hjärnan och på huden och hjärntumör är ett av raden av symptom som kan förekomma. Kognitiva svårigheter är vanligare hos dem med neurokutana syndrom än i normalbefolkningen vilket man måste ta hänsyn till när man studerar kognition efter hjärntumörer. Vissa studier har visat att kön påverkar vilka svårigheter man får och några har pekat ut kvinnligt kön som en riskfaktor.

Kognitiva svårigheter efter hjärntumör i barndomen har kopplats till förändringar i hjärnans vita substans, framför allt hos dem som fått strålbehandling. Man har funnit att större kognitiva svårigheter hänger ihop med minskad mängd vitsubstans.

Vi har idag precis börjat förstå hur långtidsförloppet för de kognitiva svårigheterna efter hjärntumör i barndomen ser ut. Tidigare studier har framför allt undersökt barn som

strålbehandlats mot hela hjärnan och funnit att de kognitiva problemen ofta ökar över åren, inte för att man går tillbaka i utvecklingen utan för att man utvecklas långsammare. Riskfaktorer för långsam utveckling är låg ålder vid diagnos, strålbehandling mot hela hjärnan, högt intrakraniellt tryck vid diagnos, kvinnligt kön och högre IQ vid diagnos.

Syftet med studierna i avhandlingen

Syftet med de fyra studierna i avhandlingen var att undersöka vilka kognitiva svårigheter personer som behandlats för hjärntumör i barndomen får, hur dessa svårigheter utvecklas över tid och vilken överensstämmelse det finns mellan bilder av hjärnan och svårigheterna. Vidare ville vi undersöka riskfaktorer för kognitiva komplikationer och för långsammare utveckling. Ytterligare ett syfte var att utvärdera neuropsykologiska uppföljningsrutiner efter barnhjärntumör. Vi sökte svar på följande frågor:

1. Vilka kognitiva svårigheter har personer som behandlats för hjärntumör?
2. Hur utvecklas svårigheterna över tid?
3. Hur ser sambandet ut mellan kognitiva svårigheter och det man ser på en avbildning av hjärnan, en magnetkamerabild?
4. Vilka riskfaktorer finns det för kognitiva svårigheter och kognitiv tillbakagång?
5. Vem får tillgång till neuropsykologiskt stöd?

Metod

Alla studierna är gjorda på Skånes Universitetssjukhus i Lund, där samtliga personer under 18 år, som bor i södra sjukvårdsregionen och som insjuknar i hjärntumör behandlas. Neuropsykolog har funnits på sjukhuset sedan 1995 och under perioden 1995-2006 erbjöds sådant stöd endast till dem som remitterats. Från 2006 startade en systematisk neuropsykologisk uppföljning med målet att alla insjuknade skulle ha möjlighet få en grundläggande bedömning. Denna uppföljning innebar att samtliga patienter fick en kort neuropsykologisk bedömning vid insjuknandet, 1, 3 och 5 år efter diagnos samt vid 18 års ålder.

I de fyra studierna undersöks sammanlagt 215 unika patienter. Under åren 1993-2013 insjuknade totalt 300 personer under 18 år i hjärntumör i södra Sverige och 275 av dem överlevde mer än ett år. Detta innebär att avhandlingens studier omfattar 78% av de patienter som diagnosticerats under 21 år och överlevt mer än ett år.

Följande metoder användes för respektive studie:

Studie 1: Gjordes för att undersöka vem som fått tillgång till neuropsykologiskt stöd. Journaldata samlades in för alla 132 patienter som insjuknat 1993-2004 och de 64 patienter som fått neuropsykologiskt stöd jämfördes med de 68 som inte fått det.

Studie 2: Gjordes för att för att undersöka vilka kognitiva svårigheter patienterna fått efter sin hjärntumör och vilka faktorer som hade samband med dessa svårigheter. Journaldata för alla patienter som fått en neuropsykologisk bedömning 1995-2006 samlades in. Dessa data undersöktes sedan med en statistisk metod (multipel linjär regression) som innebär att man undersökte vilka faktorer som samvarierar med resultaten på kognitiva tester.

Studie 3: Gjordes för att undersöka sambandet mellan kognitiva svårigheter och en hjärnavbildning, d.v.s. en bild från en magnetkameraundersökning (MR-bild). Patienter som insjuknat 1995-1998, inbjöds till en studie 10-13 år senare och 16 personer valde att delta. Dessa deltagare fick göra omfattande neuropsykologiska test och genomgå en magnetkameraundersökning. Dessa två undersökningar jämfördes med varandra på två sätt, dels ett där grupper jämförs statistiskt med varandra, dels ett mer individualiserat sätt, där neuropsykolog och neuroradiolog gemensamt diskuterade varje individ och tog hänsyn till samtliga data som fanns om varje enskild deltagare.

Studie 4: Gjordes för att undersöka hur de som haft hjärntumör i barndomen utvecklas kognitivt över tid och vilka faktorer som samvarierade med en negativ utveckling. Samtliga patienter som insjuknat 2001-2013 och överlevt mer än ett år, ingick i studien samt de patienter som fyllde 18 år 2006-2013. Tillsammans undersöktes 173 patienter som bedömts neuropsykologiskt vid 433 olika tillfällen. Data från dessa bedömningar samlades in och analyserades med en statistisk metod, multilevel mixed models. Denna metod är en utökad form av linjär regression där man förutom att se vilka faktorer som samvarierar med varandra också kan analysera varje individs utveckling över tid.

Resultat

Studie 1 visade att de som remitterades för neuropsykologisk undersökning hade större tumörer, fler recidiv och oftare högt intrakraniellt tryck vid diagnos, men i övrigt fanns inga skillnader mellan grupperna. Många av dem som inte remitterades hade riskfaktorer för kognitiva svårigheter, t.ex. hade de strålbehandlats och flera av dem hade också kognitiva svårigheter dokumenterade i den medicinska journalen.

Studie 2 visade att patienterna vid den neuropsykologiska utredningen hade generellt sänkt IQ och svårigheter med exekutiva funktioner, minne, uppmärksamhet och kognitivt tempo. Riskfaktorer för kognitiva svårigheter var strålbehandling riktad mot hela hjärnan, låg ålder vid diagnos, manligt kön och stora tumörer. Det fanns en samvariation mellan kön och tumörstorlek. Pojkar hade större tumörer än flickor bland de patienter som hade högt intrakraniellt tryck som första symptom.

Studie 3: visade att flera av patienterna som deltog i studien hade förhållandevis normala kognitiva funktioner, medan några få av dem hade ganska stora svårigheter. Både de som fått strålbehandling mot hjärnan och de som inte fått det hade förändringar i hjärnans vita substans utöver den direkta skadan som orsakats av själva tumören. Sambandet mellan MR-bilderna och kognitiva svårigheter, om man undersökte detta genom att jämföra grupper statistiskt, var inte starkt, men tydliga samband fanns om man gjord en individualiserad analys fall för fall. Fakta som gjorde att sambandet mellan MR-bilden och den kognitiva funktionen ökade var t.ex. att man vägde in data om patientens kognitiva svårigheter innan diagnos eller att man tog hänsyn till om avvikelserna fanns i särskilt sårbara områden i hjärnan.

Studie 4: visade att patienter med neurokutana syndrom hade en särskild profil och särskilda riskfaktorer och dessa uteslöts därför från vidare analys. Samtliga patientkategorier hade en avplanande utveckling över tid, d.v.s. de utvecklades inte lika snabbt som jämnåriga och fick därmed sjunkande IQ över tid. Det fanns inga riskfaktorer för en snabbare minskning av IQ över tid, däremot så fanns det flera faktorer som var relaterade till en sämre kognitiv funktion vid diagnos: manligt kön, bestrålning mot hela hjärnan, låg ålder vid diagnos, icke-central tumör i stora hjärnan och behandling med cytostatika. Två kognitiva förmågor, språkligt flöde och språklig inlärning visade sig ha en positiv utveckling över tid.

Slutsatser

Denna avhandlings 4 studier leder fram till följande slutsatser:

Studie 1: För att hitta alla patienter som behöver neuropsykologiskt stöd behöver man ha en systematisk uppföljning för samtliga patienter. Detta behövs också för att kunna utvärdera den cancerbehandling som ges, på flera olika sätt, d.v.s. inte bara genom att titta på överlevnad utan också se vilka kognitiva besvär de som överlever får. Kunskap om existerande riktlinjer för neuropsykologiskt stöd efter hjärntumör i barndomen behöver spridas.

Studie 2: Bestrålning mot hela hjärnan, stora tumörer, låg ålder vid diagnos och manligt kön är riskfaktorer för kognitiva svårigheter efter hjärntumör i barndomen. Vanliga problem är långsamt kognitivt tempo och svårigheter med exekutiva funktioner, minne och koncentration. Om man vill undersöka hur kön påverkar kognitionen efter hjärntumör måste man också ta hänsyn till att pojkar har något större tumörer vid diagnos förutsatt att det första symptomet är högt intrakraniellt tryck. Att pojkar har större tumörer beror sannolikt på deras något större huvuden.

Studie 3: Strålbehandlade såväl som icke strålbehandlade patienter har förändringar i hjärnans vita substans. Sambandet mellan dessa förändringar och kognition är komplext och beror på flera olika faktorer; vilka olika saker som påverkat hjärnan negativt, genetik,

ålder då tumören diagnostiseras och en varierande sårbarhet inom hjärnan. Studier som undersöker sambandet mellan hjärnans struktur och kognition efter hjärntumör vinner på att man kompletterar det traditionella grupp-orienterade perspektivet med ett mer individualiserat perspektiv där man försöker ta hänsyn till helheten kring varje individ.

Studie 4: Efter hjärntumör i barndomen ser man på gruppnivå en avplanande utveckling med sjunkande IQ över tid, troligtvis beroende på en långsammare utvecklingstakt. Detta gäller samtliga patientkategorier oavsett vilken behandling som givits och det finns inga särskilda riskfaktorer som påverkar utvecklingstakten. Vissa språkliga färdigheter utgör ett undantag eftersom dessa verkar förbättras över tid. Riskfaktorer för större kognitiva svårigheter vid diagnos är manligt kön, strålbehandling mot hela hjärnan, tumör i storhjärnans icke-centrala delar och behandling med cytostatika.

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Study I

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Original Article

Access to Neuropsychologic Services After Pediatric Brain Tumor

Ingrid Tonning Olsson MA [a,b,*], Sean Perrin PhD [a,e], Johan Lundgren MD, PhD [b,c], Lars Hjorth MD, PhD [b,c], Aki Johanson PhD [a,d]

[a] *Department of Psychology, Lund University, Lund, Sweden*
[b] *Department of Pediatrics, Skåne University Hospital, Lund, Sweden*
[c] *Clinical Sciences, Lund University, Lund, Sweden*
[d] *Department of Psychiatry, Lund University, Lund, Sweden*
[e] *Department of Psychology, Institute of Psychiatry, King's College, London, United Kingdom*

ABSTRACT

BACKGROUND: Increasing survival rates for children with brain tumors creates a greater need for neuropsychologic follow-up and intervention. The aim of this study was to evaluate rates of referral by medical doctors to neuropsychologic services and patient and treatment factors that differentiated referred and nonreferred patients. **METHODS:** Data were retrieved from medical records of all pediatric brain tumor patients in southern Sweden diagnosed between 1993 and 2004 who survived more than 1 year (n = 132). Characteristics of the patients, the cancer, and treatment received were then compared for patients who were and were not referred for neuropsychologic examination during that period. **RESULTS:** Sixty-four (48%) of the pediatric brain tumor patients were referred for neuropsychologic evaluation. These patients had significantly larger tumors, more recurrences of cancer, and increased intracranial pressure at diagnosis when compared with the nonreferred group (n = 68). However, most of the patients in the nonreferred group either had significant risk factors for cognitive impairment or were reporting impairments that would suggest a referral was warranted. **CONCLUSIONS:** Given the high rates of cognitive impairment in children with brain tumors, referral to neuropsychologic services should be considered in all survivors. In addition to improving long-term adjustment, systematic referral can provide data on cognitive impairments, making it possible to evaluate different cancer treatment protocols not only in terms of survival but also in terms of quality of survival. Greater efforts are needed to disseminate and raise awareness about published guidelines on the long-term care of pediatric brain tumor patients.

Keywords: pediatric brain tumor, neuropsychology, cognition, rehabilitation, neuropsychological services

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Introduction

The annual incidence of pediatric brain tumors in Sweden is 4.2 per 100,000 children (0-16 years of age) and the 10-year survival rate is approximately 72%.[1] However, many pediatric brain tumor patients suffer from long-term physical and cognitive impairments,[2–5] including deficits of attention, memory, tempo, and executive function.[6–10] Two primary risk factors for cognitive impairments in children with pediatric brain tumors are age at diagnosis (<5 years) and treatment with cranial radiation therapy (CRT).[11–14] Other identified risk include treatment with intrathecal chemotherapy, localization and type of tumor, surgery and complications from surgery (e.g. bleeding, infection), periods of increased intracranial pressure (ICP), cerebrovascular complications, and female gender.[3,4,15]

With a growing body of evidence demonstrating the risk for long-term cognitive impairments in pediatric brain tumor survivors, in 2007 the North American Children's Oncology Group recommended that "the developmental status of survivors, including their education and vocational progress and their general adaptive functioning, should be assessed annually by their primary health care provider."[16] This same group also recommended neuropsychologic

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* Communications should be addressed to: Olsson; Department of Pediatrics; Skåne University Hospital; SE-22185 Lund, Sweden.
E-mail address: ingrid.tonning-olsson@skane.se

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follow-up for all pediatric brain tumor patients from the first point of contact with a long-term follow-up program, when starting a new school, and whenever difficulties in school or wider psychosocial functioning are observed.[16] In 2003, the Swedish Working Group for Pediatric Central Nervous System Tumors developed guidelines recommending neuropsychological evaluation before surgery (if possible), and at 1, 3, and 5 years after diagnosis (unpublished position paper available from Dr. Bo Strömberg, Uppsala). Efforts are under way to harmonize guidelines across countries but there is a general recognition that systematic assessment of neurocognitive deficits is a priority for children with cancer.[17]

The Department of Pediatrics, Skåne University Hospital, Lund, Sweden, treats 15% of all children diagnosed with pediatric brain tumor nationwide. Neuropsychologic resources have been available at the department since 1995 but systematic neuropsychologic screening of all pediatric brain tumor patients was not carried out until 2007. The aim of this study was to investigate rates of referral for neuropsychologic examination between 1995 and 2006 and factors that may have influenced the decision to refer.

Patients and Methods

Patients

Between 1993 and 2004, 152 children (age 0-18 years) were diagnosed with a pediatric brain tumor at the Department of Pediatrics, Skåne University Hospital. Patients who died within 1 year of diagnosis (n = 20) were excluded from our analyses because they were usually so physically ill that a neuropsychologic evaluation was simply not indicated. Thus the final sample available for analyses was 132 survivors of pediatric brain tumors. All pediatric brain tumor patients living in the southern region of Sweden (with approximately 1.7 million inhabitants) are treated in this department, representing 15% of the Swedish population of pediatric brain tumor patients. The types of cancer, gender ratio (slightly more boys than girls), and 1-year survival rate for this regional sample was extremely similar to those reported for the country as a whole in the Swedish Childhood Cancer Registry.[18] One notable exception was that patients in the present sample had a higher percentage of astrocytomas, which may reflect the fact that patients who survived less than 1 year after diagnosis were excluded (n = 20; 10 with medulloblastomas, 6 with pons or brainstem glioma, and 4 with high-grade astrocytoma, ependymoma, or oligodendroglioma).

This study was approved by the Swedish ethical vetting board of Lund.

Data collected

All data were taken from the medical records at the Department of Pediatrics, Skåne University Hospital, including the additional neuropsychologic reports available for the 64 patients who were referred for neuropsychological evaluation. The two groups of pediatric brain tumor patients (referred and nonreferred patients) were compared on the following variables: age at first diagnosis, gender, treatment, classification and localization of tumor (infra-/supratentorial), size of the tumor at diagnosis (largest diameter in centimeters), death within the study period, increased ICP at diagnosis, ventriculoperitoneal shunt or ventriculostomy, neurocutaneous syndromes (neurofibromatosis or tuberous sclerosis), medication, and epilepsy (Table). Treatment was coded as four (nonexclusive) dichotomous variables (0 or 1): surgery, chemotherapy, CRT, and whole brain radiation therapy. Tumor classification was made according to the World Health Organization's third International Classification of Childhood Cancer,[19] but for the purposes of the present analyses these were recoded as either astrocytoma or non-astrocytoma. A patient was coded as having epilepsy if he or she had an explicit diagnosis in the medical records and the seizures were not solely the initial symptoms of a pediatric brain tumor. Medications recorded were either hormone replacement therapy or antiepileptic drugs given at any point within the study period. The children received other medications but only these two were frequent and interesting enough.

TABLE.
Characteristics of and comparison between the referred and nonreferred patients

	Examined Patients (n = 64)	Not Examined Patients (n = 68)	Total Group (n = 132)	*P* Value
Girls	34	24	58	.053
Average age at first diagnosis	8.14	8.98	8.57	.31
Astrocytoma	30	40	70	.22
Treatment given				
Surgery	60	61	121	.53
Chemotherapy	24	17	41	.14
Locally administered CRT	37	28	65	.081
Whole brain RT	11	7	18	.31
Average size of tumor at diagnosis (widest diameter)	3.85 cm	3.10 cm	3.46 cm	.015
Increased ICP at diagnosis	39	23	62	.003
Deceased at the end of year 2006	5	9	14	.40
One or more relapses	28	15	43	.010
Neurocutaneous syndromes*	5	9	14	.40
Ventriculoperitoneal shunt or ventriculostomy	11	8	19	.46
Epilepsy	7	8	15	1.00
Medication				
Hormone replacement therapy	22	20	42	.58
Antiepileptic drugs	8	11	19	.62
Infratentorial/supratentorial tumor	33/31	28/40	61/71	.30
Cognitive impairment, IQ <70	8	8	16	.84
Cognitive impairment, IQ <80	8	7	15	

Abbreviations:
CRT = Cranial radiation therapy
ICP = Intracranial pressure
RT = Radiotherapy
* Eleven patients with neurofibromatosis I, two patients with neurofibromatosis II; and one patient with tuberous sclerosis.

For patients who were referred for neuropsychologic examination, they were coded as having cognitive impairment with an IQ <70 if this diagnosis was clearly stated in the neuropsychologic report. A referred patient with IQ <80 and severely disabling learning difficulties was coded as having cognitive impairment with IQ <80. For patients who were not referred (i.e., only the medical records were available for inspection), available data on cognitive ability were extremely limited and type of schooling was used as a proxy where appropriate. In Sweden, there are two main types of compulsory schools: one for children of normal ability and one for children with a diagnosis of cognitive impairment with IQ <70. Pediatric brain tumor patients who were not referred for neuropsychologic examination were coded as having cognitive impairment if their medical records indicated that they had previously been assessed and found to have an IQ <70 and/or they attended a compulsory school for children with such learning disabilities. Patients who had been considered for the compulsory school for learning disabilities but who had not attended were coded as having cognitive impairment with an IQ <80.

Statistical methods

All statistical comparisons were carried out using IBM SPSS 20.0.[20] Differences between referred and nonreferred patient were assessed with t test for continuous variables and λ^2 test for categorical variables.

Results

Approximately half of the diagnosed patients (n = 64) were referred for neuropsychologic examination during the inclusion period (1995-2006). Patients were referred mostly by their pediatric neurologists. The main reason for referral was that a parent, teacher, or member of the medical team observed what appeared to be significant cognitive impairments. Patients were also referred when the child was at high risk of cognitive deficits because of the nature of their cancer treatment (i.e., CRT) or age at diagnosis (i.e., <5 years of age).

Pediatric brain tumor patients who were referred for neuropsychologic examination were significantly more likely to have suffered from larger tumors, increased ICP at the time of diagnosis, and recurrences of their cancer (Table). No other significant differences were observed between the two groups. Of note, the two groups did not differ on a range of potential risk factors for cognitive impairment (age at diagnosis, treatment type), suggesting that these factors played may have played a lesser role in the decision to refer. In addition, 15 of the 68 nonreferred patients (22%) contained references in their medical records to either an IQ <80 and/or referral to or attendance at a compulsory special education school.

Discussion

The present study was undertaken to identify the rate of referral to neuropsychologic services in a representative sample of children with pediatric brain tumors and to identify differences between referred and nonreferred patients. Consistent with the literature on risk for cognitive impairment following a diagnosis of pediatric brain tumor, patients in the referred group had larger tumors at diagnosis, increased ICP, and more relapses of cancer before referral. However, a significant proportion of patients who were not referred also had risk factors for cognitive impairment around the time of their diagnosis or after treatment of pediatric brain tumors. For example, 10% of patients in the nonreferred group had whole brain radiation therapy and 41% had locally administered CRT. In addition, 22% of the nonreferred patients in this nonreferred group had intellectual impairment with an IQ <80 in their medical records. At the time these patients were treated for cancer, only a few pediatric cancer centers in Sweden had access to neuropsychologic services and none of these services had the resources to screen all pediatric brain tumor patients or indeed to offer remedial treatment for those who were referred, which may have influenced the observed referral rate. It is also possible that a referral was not necessary for pediatric brain tumor survivors who were already enrolled in compulsory special education.

This is the first study to evaluate referral practices with pediatric brain tumor survivors. Nevertheless, our findings are in keeping with the results of a larger Swedish study of 526 adult survivors of central nervous system tumors and 550 of their parents.[21] In that study, Hovén et al. found that 41% of those who indicated that they had a health care need, reported that their needs went unmet, especially in the psychosocial services domain. One of the most frequent specific unmet health care needs was requests from patients and parents for counseling regarding educational or behavioral problems. Thus the present study adds to a growing body of literature indicating that access to neuropsychologic services is a priority for cancer survivors and particularly those with pediatric brain tumors.[22]

As suggested by international guidelines on the care of pediatric brain tumors, making neuropsychologic services available to every pediatric brain tumor patient is likely to improve long-term outcomes. Greater efforts are needed to disseminate these guidelines and ensure compliance. In addition, data collected from systematic neuropsychologic assessments of cancer survivors should be placed in national registries to help evaluate the long-term effects of various treatment protocols, because newer treatments are emerging that are designed to spare normal brain tissues from radiation (e.g., proton beam therapy[23]).

Limitations

All data were collected retrospectively from the medical records; thus, the authors had little control over specificity or accuracy. In contrast to the reports of the neuropsychologic examination, the patients' medical records had very limited information on cognitive ability (i.e., the terms “mental retardation” or “compulsory special needs schooling” were referenced but not the specific IQ scores or the extent of the child's learning difficulties). We used references to special needs schooling as a proxy for cognitive impairment when only references to the former were present in the medical records.

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Study II

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Original Article

Long-Term Cognitive Sequelae After Pediatric Brain Tumor Related to Medical Risk Factors, Age, and Sex

Ingrid Tonning Olsson MA [a,b,*], Sean Perrin PhD [a,c], Johan Lundgren MD, PhD [b,d], Lars Hjorth MD, PhD [b,d], Aki Johanson PhD [a,e]

[a] *Department of Psychology, Lund University, Lund, Sweden*
[b] *Department of Pediatrics, Skåne University Hospital, Lund, Sweden*
[c] *Department of Psychology, Institute of Psychiatry, King's College London, London, United Kingdom*
[d] *Department of Clinical Sciences, Lund University, Lund, Sweden*
[e] *Department of Psychiatry, Lund University, Lund, Sweden*

ABSTRACT

BACKGROUND: Young age at diagnosis and treatment with cranial radiation therapy are well studied risk factors for cognitive impairment in pediatric brain tumor survivors. Other risk factors are hydrocephalus, surgery complications, and treatment with intrathecal chemotherapy. Female gender vulnerability to cognitive sequelae after cancer treatment has been evident in some studies, but no earlier studies have related this to tumor size. The purpose of our study was to find factors correlated with lowered IQ in a nationally representative sample of pediatric brain tumor patients referred for neuropsychologic evaluation. **METHODS:** Sixty-nine pediatric brain tumor patients, diagnosed 1988-2005 and tested 1995-2006, were included in the study. In a series of stepwise multiple regressions, the relationship of IQ to disease, treatment, and individual variables (sex and syndromes) were evaluated. A subanalysis was made of the covariation between sex and tumor size. **RESULTS:** The patients had generally suppressed IQ and impairments in executive function, memory, and attention. Lowered IQ was associated with young age at diagnosis, being male, tumor size, and treatment with whole-brain radiation therapy. A sex difference was evident for patients with increased intracranial pressure at diagnosis with males having larger tumors. Tumor size was found to be a better predictor of cognitive sequelae than sex. **CONCLUSIONS:** Whole-brain radiation therapy, large tumors, young age at diagnosis, and male gender are risk factors for late cognitive sequelae after pediatric brain tumors. When examining sex differences, tumor size at diagnosis needs to be taken into account.

Keywords: pediatric brain tumor, cognition, sex, whole-brain radiation therapy

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Introduction

Pediatric brain tumors (PBTs) are the most common solid tumors in children under 18 years of age. In Sweden, the annual PBT incidence is 4.2 per 100,000 in children aged 0-16 years, with a 5-year survival rate of 76%.[1] Improved treatments for PBT have resulted in a growing group of survivors with varying degrees of physical and cognitive impairment, many of whom will need rehabilitation and societal support.[2,3] Identification of risk factors for cognitive impairment can play an important role in treatment planning at the time of cancer diagnosis and in management of survivors at risk for developing cognitive impairments.

The most common cognitive deficits in PBT survivors involve attention, memory, cognitive processing speed, executive function, and spatial ability.[4-8] A number of follow-up studies of PBT survivors strongly suggest that early age at diagnosis and treatment with cranial radiation therapy (CRT) significantly increase the risk of cognitive impairment.[9-11] Other risk factors include localization and type of tumor; periods of increased intracranial pressure

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* Communications should be addressed to: Tonning Olsson; Department of Pediatrics; Skåne University Hospital; SE-22185 Lund, Sweden.
E-mail address: ingrid.tonning_olsson@med.lu.se

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TABLE 1.
Characteristics of the Study Group (n = 69)

Variable	Average/Frequency	Standard Deviation	Range
Girls/Boys	36/33		
Average age at first diagnosis (yr)	8.01	4.35	0.81-17.37
Type of tumor, WHO ICCC-III*			
IIIa, Ependymomas and choroid plexus tumors	10		
IIIb, Astrocytomas	34		
IIIc, Intracranial and intraspinal embryonal tumors	9		
IIId, Other gliomas	5		
IIIe, Other specified intracranial and intraspinal neoplasms	11		
Treatment given			
Surgery	63		
Chemotherapy	24		
Partial CRT	40		
Whole-brain RT	11		
Average size of tumor at diagnosis (widest diameter, cm)	3.80	1.69	0.9-8.0
Increased ICP at diagnosis	41		
One or more relapses	30		
Neurocutaneous syndromes†, neurofibromatosis, or tuberous sclerosis	7		
Ventriculoperitoneal shunt or ventriculostomy	13		
Epilepsy	7		
Infratentorial/supratentorial tumor	35/34		
Average time elapsed between diagnosis and testing (yr)	4.58	3.31	0.09-12.79
Average age at testing (yr)	12.61	4.07	4.34-20.57

Abbreviations:
CRT = Cranial radiation therapy
ICP = Intracranial pressure
RT = Radiation therapy
* World Health Organization: International Classification of Childhood Cancer, third edition.
† Four patients with neurofibromatosis 1; two patients with neurofibromatosis 2; one patient with tuberous sclerosis complex.

(IICP); cerebrovascular complications, surgery, and complications from surgery (e.g., bleeding or infection); treatment with intrathecal chemotherapy and/or dexamethasone; use of a ventriculoperitoneal shunt; time since treatment; and being female.[12–14] Understanding how these various risk factors interact to impair cognitive functioning is complicated by the direct and indirect ways that tumors and treatment can cause damage to brain tissue.[15] The tumor itself, hydrocephalus, surgery, and related complications, as well as any subsequent cancer treatment, might all contribute to a negative cognitive outcome.[16] An additional factor complicating our understanding of risk for cognitive impairment is that around 10% of PBT patients have neurocutaneous syndromes (neurofibromatosis and tuberous sclerosis) that can cause cognitive impairments.[17] The purpose of the present study was to examine the relative contribution of risk factors for cognitive impairment in a representative sample of PBT patients observed at a specialist center in Sweden over a 12-year period.

Patients and Methods

Patients

The children in this study were diagnosed with a PBT at the Department of Pediatrics, Skåne University Hospital, Lund, Sweden, between 1988 and 2005. They received some form of support from the Neuropsychology Department at the same hospital between 1995 and 2006. Between 1995 and 2006, a total of 110 children (0-20 years old) had some contact with the neuropsychology services. Of these, 40 underwent a short interview with no psychometric assessment or had a very short neuropsychologic screen because they were too sick to undergo a full assessment or were about to have immediate surgery. These 40 patients were excluded together with a patient who was severely cognitively challenged and therefore had got a the Bayley-II test[18] highly out of her age range, leaving a total of 69 patients who had more complete posttreatment neuropsychologic data available for study.

Diagnostic characteristics of the 69 patients are presented in Table 1. The neuropsychologic evaluation occurred at an average age of 12.6 years (standard deviation [SD], 4.1 years; range, 4.3-20.6 years) and at an average of 4.6 years after diagnosis (SD, 3.3 years; range, 0.1-12.8 years). The patients were referred for neuropsychologic examination by the treating medical doctor (mostly a pediatric neurologist) because of cognitive problems reported by the parents, the teacher, or the medical doctor or because the child had been exposed to known risk factors for cognitive impairment such as CRT or early age at PBT diagnosis.

Data collection

Data were obtained from the patients' medical and neuropsychologic records at the Department of Pediatrics where they were treated for the PBT. Records were reviewed to identify risk factors for cognitive impairment in children with PBTs: age at first PBT diagnosis, sex, classification and localization of tumor, size of the tumor at diagnosis (largest diameter in cm), neurocutaneous syndromes (tuberous sclerosis or neurofibromatosis), epilepsy, treatment type, hydrocephalus at diagnosis, and use of a ventriculoperitoneal shunt or ventriculostomy (Table 1).

Treatment, tumor localization, and classification

Treatment was coded as four dichotomous (0 or 1) nonexclusive variables: surgery, chemotherapy, CRT, and whole-brain radiation therapy (WBRT). Tumors were classified according to the World Health Organization's International Classification of Childhood Cancer III[19] but entered into analyses as either nonastrocytoma (0) or astrocytoma (1). Tumor localization was coded as infratentorial or supratentorial.

Cognitive measures

All neuropsychologic evaluations were carried out by neuropsychologists working in the Pediatric Neuropsychology Service at Skåne

TABLE 2.
Test Used in the Neuropsychologic Evaluation, Only Test Used for More Than Nine Evalulations

Test	Number of Patients Tested
WISC-III	48
Nepsy, word fluency	36
Nepsy, memory for names	33
Nepsy, word list memory	29
Rey-Osterrieth Complex Figure test	29
Nepsy, comprehension of instructions	28
Nepsy, narrative memory	28
Nepsy, speeded naming	26
Nepsy, visual attention	18
Benton Visual Retention Test	17
Nepsy tower of London	14
Nepsy, auditory attention	11
WPPSI-R	10
WAIS-R or WAIS-III	10
Nepsy, design fluency	10

Abbreviations:
WAIS = Wechsler Adult Intelligence Scale
WISC = Wechsler Intelligence Scale for Children
WPPSI = Wechsler Preschool and Primary Scale of Intelligence

University Hospital using standardized measures. Each patient got an age-appropriate Wechsler test (age, <6 years: Wechsler Preschool and Primary Scale of Intelligence [WPPSI]; age, 6-16 years: Wechsler Intelligence Scale for Children [WISC]; age >16 years: Wechsler Adult Intelligence Scale [WAIS]) and several other neuropsychologic test chosen to measure each individual's special difficulties, mostly some of the Nepsy[20] subtests, Rey Complex Figure test,[21] or Benton Visual Retention Test.[22] (See Table 2 listing all test used for 10 evaluations or more.) Only measures from the Wechsler test were used in the analysis of risk factors. If the patient underwent more than one neuropsychologic examination, only the most recent test scores were used in the analyses. Most of the patients, n = 56, had got a WPPSI-III,[23] a WISC-III,[24] or a WAIS-III[25] generating the following measures: full-scale IQ (FIQ), verbal IQ (VIQ), performance IQ (PIQ), verbal comprehension index (VCI), perceptual organization index, freedom from distractibility, and processing speed index (PSI).[24] Thirteen patients had got the earlier versions of WPPSI and WAIS, i.e., WPPSI-R[26] and WAIS-R,[27] and for those patients, the only measures available were FIQ, PIQ, and VIQ.

Other indicators of cognitive functioning

The neuropsychologic examination was summarized in a report for 63 of the 69 patients. Each report had a summarizing section with the neuropsychologist's evaluation of the child's cognitive functioning. This evaluation was based on all test results (including the neuropsychologic tests mentioned in Table 2), interview with the parents and the child's teacher, and data available in the records. Each problem mentioned in the evaluation section was recorded and then sorted into 11 different categories (examples within parenthesis): executive dysfunction (low emotional control and vulnerable to cognitive overload), attention difficulties and/or hyperactivity (lacking endurance, impulsive, and Attention Deficit/Hyperactivity Disorder), mental retardation and/or generally reduced cognitive capacity (difficulties with abstract reasoning and mental retardation), slow cognitive processing, memory difficulties, language difficulties, academic failures (dyslexia and dyscalculia), difficulties in relationship to peers (not appropriate distance to strangers, assertive, and boasting), emotional difficulties (depressed), reduced motor skills, and visuospatial perception difficulties.

Statistical methods

All analyses were carried out using SPSS Version 20.0.[28] In a first step, all potential risk factors (independent variables in the linear regression) were correlated with FIQ and only variables correlated with FIQ at $P < 0.25$ were used in subsequent stepwise linear regressions (backwards entry). This was performed to avoid too many independent variables. In the regression model, variables were removed when $P > 0.05$. To analyze the relation between the two independent variables, sex and tumor size, a first step was to test the hypothesis that boys have larger tumor at diagnosis because they have larger head circumference making the tumor grow larger before signs of hydrocephalus appear. This was performed with two two-tailed Student *t* test for children with or without hydrocephalus at diagnosis, respectively. To examine any further possible interactions between sex and tumor size, two different analyses were made: univariate correlations and a linear regression model using sex, tumor size, and tumor size × sex (interaction variable) as independent variables. An extended analysis was also made for this model using the Johnson-Neyman technique. The technique analyzes the influence on the dependent variable (IQ) by one or more of the independent variables (sex) along the continuum of a moderating variable (tumor size).[29]

TABLE 3.
Neuropsychologic Measures, IQ Values With Norms Mean = 100 and Standard Deviation = 15

Cognitive measure	Mean	Standard Deviation	n	Minimum	Maximum
Full-scale IQ	87.03	21.93	69	37	127
Verbal IQ	90.80	19.08	69	42	126
Performance IQ	85.55	23.76	69	32	144
Verbal comprehension index	91.54	16.16	56	50	120
Perceptual Organization Index	89.25	19.98	55	49	137
Freedom from distractibility	87.02	18.53	55	48	131
Processing speed index	82.36	20.25	56	47	147

Results

Descriptives

Table 3 presents descriptive statistics for IQ in the sample. The group as a whole revealed a generally reduced IQ with average scores 0.75-1.0 SDs below the mean for the relevant age and/or sex normative group. Lowest average IQ scores were on PSI and highest on VIQ; however, the difference between the different indices were quite small (8.4 IQ points). Table 4 presents the frequency of cognitive and psychosocial problems identified by the neuropsychologist at the time of assessment with the most frequent being

TABLE 4.
Problems Mentioned in the Neuropsychologic Reports

Problem category	Number of Reports	%
Executive dysfunction	34	49.28
Memory difficulties	34	49.28
Slow cognitive processing	26	37.68
Attention difficulties and/or hyperactivity	25	36.23
Mental retardation and/or generally reduced cognitive capacity	14	20.29
Language difficulties	12	17.39
Visuospatial perception difficulties	12	17.39
Academic failures	10	14.49
Reduced fine or gross motor skills	7	10.14
Difficult relationship to others	4	5.80
Emotional difficulties and/or depression	1	1.45

TABLE 5.
Linear Regression Models for Different IQ Measures

Dependent Variable	Explained Variance (%)	Variables Included in the Model	Unstandardized Coefficients		Standardized Coefficients	
			B	Standard Error	β	*P*
Full-scale IQ, n = 69	29.8	Constant	84.20	5.52		
		Sex	−12.26	4.55	−0.28	0.009
		Whole-brain radiation therapy	−20.28	6.18	−0.34	0.002
		Age at first diagnosis	1.49	0.53	0.30	0.009
Verbal IQ, n = 69	29.4	Constant	94.40	6.85		
		Tumor size	−2.65	1.22	−0.24	0.034
		Whole-brain radiation therapy	−17.25	5.47	−0.33	0.002
		Age at first diagnosis	1.15	0.47	0.26	0.017
Performance IQ, n = 69	25.3	Constant	84.72	6.17		
		Whole-brain radiation therapy	−19.68	6.91	−0.31	0.006
		Age at first diagnosis	1.33	0.59	0.24	0.027
		Sex	−14.01	5.08	−0.31	0.008
Verbal comprehension index, n = 56	27.0	Constant	98.61	2.76		
		Whole-brain radiation therapy	−16.39	5.50	−0.38	0.001
		Sex	−7.89	3.76	−0.25	0.041
Perceptual organization index, n = 55	19.0	Constant	97.45	3.61		
		Whole-brain radiation therapy	−20.01	7.03	−0.36	0.006
		Sex	−11.18	4.97	−0.28	0.029
Freedom from distractibility index, n = 55	24.6	Constant	77.75	5.51		
		Whole-brain radiation therapy	−19.82	6.28	−0.38	0.003
		Age at first diagnosis	1.43	0.58	0.30	0.017
Processing speed index, n = 56	27.0	Constant	92.60	3.44		
		Whole-brain radiation therapy	−24.62	7.19	−0.41	0.001
		Sex	−15.44	4.77	−0.38	0.002

Stepwise linear regression, backward entry of variables. Variables removed at $P > 0.05$.
Variables entered at step 1: Age at diagnosis, chemotherapy, radiation therapy, whole-brain radiation therapy, increased intracranial pressure at diagnosis, ventricular peritoneal shunt or ventriculostomy, sex (female = 0, male = 1), tumor size (largest diameter in cm), astrocytoma, and time between diagnosis and testing.

executive dysfunction and difficulties with memory, followed by slow cognitive processing and AD/HD. Only four of the patients (5.8%; all girls) had normal cognitive functioning.

Analysis of risk factors

Of 15 proposed risk factors (age at diagnosis, recurrence, surgery, chemotherapy, focal CRT, WBRT, hydrocephalus at diagnosis, infratentorial tumor, neurocutaneous syndromes, epilepsy, ventriculoperitoneal shunt, sex, size of tumor, astrocytoma, and time from diagnosis), 10 were correlated with FIQ with $P < 0.25$. Excluded variables were recurrence, surgery, infratentorial tumor, neurocutaneous syndromes, and epilepsy. Table 5 presents the results of the linear regression analyses. WBRT was most strongly and negatively correlated with performance across IQ measures. Being younger was associated with lower FIQ, VIQ, PIQ, and freedom from distractibility, whereas male sex was associated with lower FIQ, PIQ, VCI, perceptual organization index, and PSI. Tumor size was negatively correlated with only VIQ.

TABLE 6.
Gender Differences in Tumor Size Related to Increased Intracranial Pressure at Diagnosis (IICP), Two-Tailed Student *t* Test

Variable	IICP at Diagnosis			No IICP at Diagnosis		
	Males	Females	*P*	Males	Females	*P*
Average tumor size (cm)	4.9	3.5	0.007	3.3	3.0	0.60

Extended analysis of sex and tumor size

A covariation was found among the independent variables: boys had larger tumors than girls at PBT diagnosis (4.4 versus 3.4 cm; $P = 0.015$). This was hypothesized to be caused by boys having a larger head circumference, i.e., larger volume of the skull allows a tumor to grow larger before signs of hydrocephalus appear. This hypothesis was confirmed when patients with and without IICP at diagnosis was analyzed separately concerning tumor size and sex (Table 6). Among children who had IICP at diagnosis, the sex difference in tumor size was highly significant, but among children without IICP at diagnosis, no such difference

TABLE 7.
Correlations Between Different IQ Measures, Sex, and Tumor Size

Cognitive measure	Largest Diameter (cm) at Diagnosis	Sex
Full-scale IQ		
Pearson correlation	−0.373	−0.301
p (two tailed)	0.002	0.012
n	69	69
Verbal IQ		
Pearson correlation	−0.352	−0.230
p (two tailed)	0.003	0.057
n	69	69
Performance IQ		
Pearson correlation	−0.376	−0.313
p (two tailed)	0.001	0.009
n	69	69

Male = 1, Female = 0.

TABLE 8.
Linear Regression Models With Tumor Size, Sex, and Size × Sex Predicting IQ

Dependent Variable, n = 69	Explained Variance (%)	Variables Included in the Model	Unstandardized Coefficients		Standardized Coefficients	*P*
			B	Standard Error	β	
Full-scale IQ	19.1	Constant	111.46	7.53		
		Sex	−22.25	12.96	−0.51	0.091
		Tumor size	−5.55	2.06	−0.43	0.009
		Interaction sex × size	3.48	3.07	−0.39	0.26
Verbal IQ	16.9	Constant	112.49	6.64		
		Sex	−20.93	11.42	−0.55	0.071
		Tumor size	−5.35	1.82	−0.48	0.004
		Interaction sex × size	4.14	2.71	0.53	0.13
Performance IQ	19.1	Constant	110.95	8.16		
		Sex	−21.26	14.03	−0.45	0.135
		Tumor size	−5.60	2.23	−0.40	0.014
		Interaction sex × size	2.90	3.32	−0.30	0.39

existed. Further analysis was performed with simple correlations and a linear regression model with tumor size, sex, and an interaction variable, sex × size, for predicting FIQ, VIQ, and PIQ (Tables 7 and 8). These analyses revealed tumor size to be a slightly better predictor of IQ than sex. Using the Johnson-Neyman technique for probing interactions in linear models, sex was found to significantly contribute to explained variance in IQs when tumors were between 2.1 and 3.2 cm for FIQ and between 2.9 and 3.2 cm for PIQ (Table 9).

Discussion

This is one of the larger studies to examine potential risk factors for cognitive impairment in Swedish children who have survived PBTs combining both qualitative and quantitative measures and the first study to examine the relation between tumor size and sex. Consistent with previous studies of IQ in PBT survivors, the study patients had generally lowered IQ. The differences between the average IQ indices were small but still revealed a profile in line with previous studies with lowest average score on PSI and highest scores on VCI.[30,31] The qualitative evaluations of all test results and data from other sources revealed that the survivors had impairments in executive function, memory, and attention and that very few patients had no signs of cognitive impairment whatsoever. This is well in line with previous findings, and it also reveals the importance of using more cognitive measures than IQ. Four variables were most strongly related to cognitive impairment: WBRT, sex, tumor size, and age at diagnosis.

TABLE 9.
Johnson-Neyman Analysis Revealing How Well Gender Predicts Full-Scale IQ Along the Continuum of Tumor Size

Tumor Size	*B*	Standard Error	*T*	*P*
0.90	−19.12	10.48	−1.82	0.07
1.26	−17.88	9.54	−1.87	0.07
1.61	−16.65	8.65	−1.93	0.06
1.97	−15.41	7.80	−1.98	0.05
2.12	−14.86	7.44	−2.00	0.05
2.32	−14.17	7.02	−2.02	0.05
2.68	−12.94	6.32	−2.05	0.04
3.03	−11.70	5.76	−2.03	0.05
3.23	−11.00	5.51	−2.00	0.05
3.39	−10.46	5.36	−1.95	0.06
3.74	−9.23	5.16	−1.79	0.08
4.10	−7.99	5.19	−1.54	0.13
4.45	−6.76	5.44	−1.24	0.22
4.81	−5.52	5.88	−0.94	0.35
5.16	−4.28	6.48	−0.66	0.51
5.52	−3.05	7.19	−0.42	0.67
5.87	−1.81	7.99	−0.23	0.82
6.23	−0.57	8.85	−0.06	0.95
6.58	0.66	9.76	0.07	0.95
6.94	1.90	10.70	0.18	0.86
7.29	3.13	11.67	0.27	0.79
7.65	4.37	12.66	0.35	0.73
8.00	5.61	13.66	0.41	0.68

Male = 1, Female = 0. Significant effects of sex are revealed only for tumor sizes 2.12-3.23 cm.

WBRT and age

In the present study, WBRT was associated with cognitive impairment as opposed to localized radiation therapy which was not. In several previous studies, no distinction is made between localized and WBRT in relation to subsequent cognitive impairment even if this is quite well documented.[32,33] However, since WBRT often is given in combination with chemotherapy and primarily to patients with medulloblastomas and more malignant tumors, it is unclear whether the cognitive impairments associated with WBRT are because of this treatment, the presence of medulloblastomas, the chemotherapy, or the interaction of the three. Additional studies are needed where the type of CRT given is specified, and where possible, to identify specific regions sensitive to radiation therapy.[34] The current findings for age are consistent with previous studies that have revealed that the younger age at diagnosis of PBT increases the risk of subsequent cognitive impairment.[35,36]

Tumor size and sex

Males had larger tumors at diagnosis given that the initial finding was IICP. Because boys have larger cranial volumes than girls,[37] this is not an unexpected finding, but it shows the importance of relating any sex differences in cognition after PBT to tumor size. Tumor size seems to be a

better predictor of cognitive sequelae than sex and sex adds predictive value only for average-sized tumors (around 3 cm diameter). It has previously been described that tumor size at diagnosis has no correlation at all with cognition at diagnosis,[38] but few studies have compared brain tumor size at diagnosis with posttreatment cognition. Brain tumor size can be observed as an underlying cause for several other following risk factors such as larger radiation field, hydrocephalus, and ventriculoperitoneal shunt. The finding that males were more vulnerable was unexpected because several previous findings reveal females to be more vulnerable.[39,40] However, in a review, Armstrong et al.[41] found that support is given for a female vulnerability to cognitive late sequelae after cancer treatment in patients with acute lymphoblastic leukemia but not in patients with brain tumors.

Armstrong et al.[41] point out that a better understanding of the biological basis for sex differences is needed. They state that hormonal differences are not a plausible explanation because those differences are small in children. Hypothesis about sex differences in DNA repair have been proposed but not proven. Our findings revealing tumor size to be relevant for predicting late cognitive sequelae in relation to sex add to those hypotheses. Larger (prospective) studies of PBT survivors are needed where sex and other potential risk factors are evaluated.

Limitations

The present study benefits from the use of a representative sample of PBT patients and standardized measures of cognitive impairment. However, the findings must be interpreted with caution provided that data were obtained retrospectively from medical and neuropsychologic records. Although a sample size of 69 is not small, the number of risk factors evaluated was large, and it is possible that additional risk factors would have been identified with a larger sample size. A prospective study of children with PBT addressing these limitations is currently underway by the lead author and funded by the Swedish Childhood Cancer Foundation.

Conclusions

This study adds to a large body of literature indicating that PBTs and their treatment markedly increase the child's risk of cognitive impairments and that younger children and those who receive WBRT appear to be at greatest risk. Tumor size is correlated with cognitive sequelae and a sex difference exists with males having larger tumors if they present with IICP at diagnosis. Any study examining gender differences in cognition after PBT need to take brain tumor size into account.

Finally some of the shortcomings of this study could have been avoided if the neuropsychologic follow-up had been systematic and had included all diagnosed patients. We must therefore underline the importance of systematic neuropsychologic follow-up of PBT survivors as recommended by the North American Children's Oncology Group.[42] Data collected from regular standardized assessments of cognitive and psychosocial functioning should be entered into national databases to assist in the evaluation of the immediate and long-term health, cognitive and psychosocial impacts of specific types of PBTs, and the various approaches used to treat them.[43]

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Hope, 1886, George Frederic Watts (1817-1904) and assistants ©Tate, London 2015.

This is **not** me writing my thesis. This is Hope, a painting from 1886 by George Frederic Watts. In Greek mythology, Pandora opened a box and let out all evil, all plagues and diseases. When she closed the box, only Hope was left inside. Hope – who might at first look as despair here – holds a lyre with only one chord. Watts himself said that "Hope need not mean expectancy. It suggests here rather the music which can come from the remaining chord". Barack Obama, president of the United States, was inspired by a sermon based on an analysis of this painting and named his second book "Audacity of Hope". The audacity of hope here refers to the ability to continue to play when the evil of the world has bereaved you of all but one chord.

Getting a diagnosis of a brain tumor as a child, might at first seem like total despair. My clinical work, my research and my thesis is all about hope, but hope without ignoring despair. I want to help my patients to understand what chords they have left, and enable them to play with the remaining chords, that is to help them create the audacity of hope.

Ingrid Tonning Olsson

LUND UNIVERSITY
Faculty of Social Sciences
Department of Psychology
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