Cognitive Impairment Subsequent to Successful Pediatric Brain Tumour Treatment – The Long-term Implications

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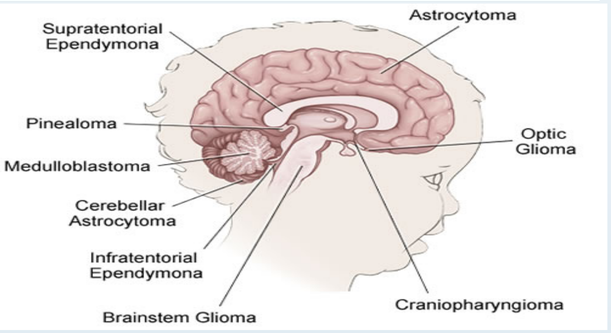
Abstract

Paediatric brain tumours were once associated with an extremely poor prognosis and high mortality rate. Advances and refinement of cancer treatment protocols have drastically changed this, and greatly ameliorated survival rates on a global scale. While many paediatric patients are fortunate enough to have their brain cancer successfully treated and are free of recurrent malignancies, they may not be able to have the same quality of life that they could have expected before their diagnosis. Research suggests that the survivors of paediatric brain tumours may suffer from an assortment of cognitive and neuropsychological deficiencies later in life, due to the nature of these tumours and the rigorous treatment that must be undergone to eradicate them. The aim of this structured review is to determine what the literature indicates in terms of the nature and progression of these cognitive deficiencies. Additional information was also collected pertaining to the predictors and risk factors for increased cognitive decline. following treatment.

Research Question

What is the nature and extent of the long-term cognitive deficiencies experienced by individuals who undergo successful treatment for common paediatric brain tumours?

Background



Locations of various common pediatric brain tumours.

Primary brain tumours are a diverse group of intracranially-originating neoplasms that account for the most solid cancer deaths among Canadians under the age of 20 (Brain tumour foundation Of Canada, 2015). In the past 30 years, the survival rate from childhood brain cancers has greatly increased however, due to significant advances in surgery, chemotherapy, and radiation therapy (Duffner, 2010). For this reason, increased emphasis is now being placed on the quality of life (QOL) of children who undergo successful treatment fort these cancers (Grill, Keiffer & Kalifa, 2004). Survivors, due to their varying degrees of physical and cognitive disabilities, require extensive rehabilitation and social support (Tonning-Olsson et al., 2014).

While revising current paediatric brain tumour literature, it became very apparent that the treatment for brain tumours causes an almost-certain decrease in Intelligence quotient (IQ) on a full-scale. What was far less evident was the nature, type, extent and degree of progression of the neurocognitive impairments associated with this fall in IQ. Ris and Noll (1994) outlined the need for more a comprehensive battery allowing testing of specific neuropsychological functions in paediatric brain tumour patients. 20 years later the literature on this topic is quite ambiguous as studies report varying degrees and types of late cognitive deficiencies associated with the treatment of paediatric brain tumours. There are discrepancies concerning the treatment – and tumour-related risk factors for greater cognitive decline as well. The lack of access to specialized educational interventions this may cause amongst children who experience deficits following brain tumour treatment may result in them not receiving the services they need to properly develop (Robinson et al.,2010). The aim of this review is to collect evidence about the nature of these impairments from multiple sources so as to shed light on the matter and facilitate the design of rehabilitation and intervention initiatives for these individuals in the future.

References

Duffner, P. K. (2010). Risk factors for cognitive decline in children treated for brain tumors. *European Journal of Paediatric Neurology, 14*(2), 106-115. doi:http://dx.doi.org/10.1016/j.ejpn.2009.10.005
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Tonning Olsson, I., Perrin, S., Lundgren, J., Hjorth, L., & Johansson, A. (2014). Long-term cognitive sequelae after pediatric brain tumor related to medical risk factors, age, and sex. *Pediatric Neurology, 51*(4), 515-521. doi:10.1016/j.pediatrneurol.2014.06.011 [doi]

Methodology

Figure 1: Flow chart Outlining database search

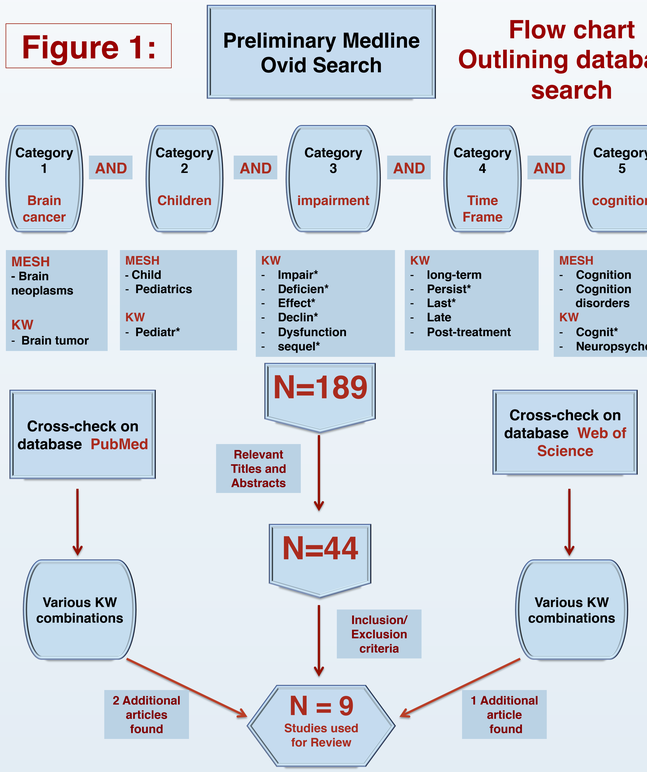

TABLE 1: INCLUSION / EXCLUSION CRIITERIA

	INCLUSION CRITERIA	EXCLUSION CRITERIA
	POPULATION	
SPECIES	Human	All other species
AGE GROUP	Children aged 2 to 18 at time of operation for tumour removal	Children outside of range
	EXPERIMENT	
FOLLOW UP TESTING	Within 10 years of treatment conclusion. (at least one year after diagnosis)	Less than 1 year or over 10 years have passed since treatment
FORM OF CANCER	**Commonly occurring brain tumours** Posterior fossa tumours: Medulloblastomas, cerebellar astrocytomas, brainstem gliomas, & ependymomas. Cerebral hemisphere tumours: astrocytomas, oligodendrogliomas, & craniopharyngiomas.	**Rare, atypical, non-localized tumour/cancer** (ex. lymphoma) **or non-intracranial CNS malignancies.**
ORIGIN OF CANCER	Primary tumour	Non-primary, originating elsewhere
CURRENT CONDITION OF PARTICIPANTS	Cancer is eradicated - Has not had a secondary malignant neoplasm develop.	Secondary malignant neoplasm developed.
MEASUREMENT	Cognitive/neuropsychological long-term effects measured (Ex.IQ, memory, attention)	Other effects are focus of measurement (Physical, endocrine)
	STUDY INFORMATION	
TYPE OF STUDY	Cross-sectional, prospective cohort, systematic review, literature review, meta-analysis, experimental	Case-control, descriptive studies, qualitative studies, case studies
PUBLICATION DATE	2000-2015	Before 2000
LANGUAGE	English	All other languages
REVIEW	Peer-reviewed	Non peer-reviewed
AVAILABILITY	Available through Medline, PubMed, & Web of Science	Not available through noted databases

Results

Figure 2: Frequency of Various Cognitive Skills/Domains Deemed Significantly Impaired in studies of Pediatric Brain Tumour Survivors

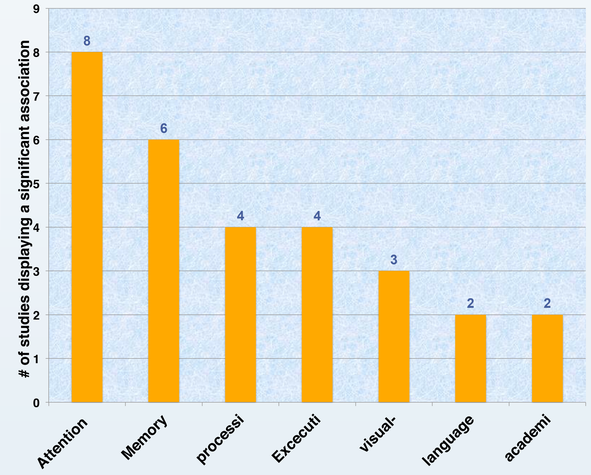

TABLE 2: Progressive nature & Predictors of Cognitive Impairment

AUTHOR	STUDY	PRESENCE OF KEY RISK FACTORS			COGNITIVE DECLINE PROGRESSES OVER TIME
		High Doses of Radiation Therapy	Very young age at time of diagnosis	OTHER	
1. Aarsen et al. (2009)	Cohort	X	X		YES
2. Briere et al. (2008)	Cohort	X		X (Chemo)	YES (Attention only)
3. Carey et al. (2001)	Cross-sectional		NR		NR
4. Divcic & Hajnzic (2008)	Cohort	X			NO (Improved)
5. Maddrey et al. (2005)	Cross-sectional		X	X	YES
6. Reimers et al. (2007)	Cross-sectional	X		X	NR
7. Robinson et al. (2010)	Meta-analysis		NR		NR
8. Olsson et al. (2015)	Cross-sectional	X (WBRT)	X	X (Sex)	NR
9. Wolfe et al. (2012)	Systematic review	X	X		YES (Some domains)

Table 3: Magnitude of Cognitve declines observed in Participants

	Hedge's g	% Of participants who presented with decline	T-score	Z-score
Attention	-1.22	- 36.23 - 85	-4.88	-1.2
Memory	-1.14	49.28		
Processing speed		37.68		-1.7
Executive functioning		- 49.28 - 82		
Visual-spatial skills	-1.14	- 74		

Discussion

Total number of participants in all studies 326 + 1318 from included meta-analysis (Study #7). From Study #7 – **Hedge's g for global late cognitive effects** of paediatric brain tumour treatment calculated using data from1318 participants **= -0.91**.

This structured review indicates that the four most prevalent cognitive deficits experienced by paediatric brain tumour survivors in order are in **1. sustained attention and freedom from distractibility**, **2. working or short-term memory**, **3. cognitive processing speed**, and **4. general executive functioning.**

Results generally favour the conclusion that these declines get progressively worse with time, at least within the 10-year window that was used as an inclusion factor for this review.

Results also strongly indicate but are not unanimous in confirming that use of radiation therapy especially whole-brain radiation therapy (WBRT) and younger age at diagnosis are the two most important risk factors for more severe cognitive deficits in paediatric brain tumour survivors.

Other prevalent risk factors mentioned in the literature include:
- Insertion of a ventriculoperitoneal (VP) shunt during treatment.
- White matter necrosis or compromise (which can be caused by RT and CT).
- Cerebral hemisphere tumour location.

STRENGTHS & LIMITATIONS

None of the studies in this review, point to a distinct neuropsychological profile of pediatric-brain tumour survivors. Commonalities in deficits are addressed but heterogeneity of sample populations makes it difficult to develop a universal and complete picture of the late cognitive effect of treatment.

Limitation is caused by the cross-sectional design of many of the studies examined. (#3, #5, #6 & #7). These studies would be more informative regarding progression of deficits if they included repeat neuropsychological testing, as well as quality of life measures at regular intervals. Only then could a more focused picture of residual deficits and their impact on daily functioning and quality of life be ascertained.

Limitations that affect most studies in this review pertain to certain threats to their internal and external validity such as history, sample size, maturation, selection, and absence of a control group.

- The selective attrition of participants due to progressive disease and death was cause of selections bias. (All studies).
- Most participants underwent polytherapy during tumour treatment. It is unknown whether or not children not undergoing polytherapy would encounter similar deficits. (All studies).
- Small sample size may be unrepresentative of population as a whole (#2, #3, #5, #8).
- Lack of comparison group from which to establish more accurate normative cognitive skill scores (#1, #3, #6,# 8).
- SES status of sample is unrepresentative of the general population (#3).

The wide-array of pediatric brain tumours included in this review made its conclusions more universal and applicable to a typical heterogeneous population. Furthermore,The repetition across studies of the associations between brain tumour treatment and certain key cognitive domains/skills and the strength of these associations is evidence that the methodology used to select studies was capable of arriving at strong conclusion regarding the research question. The capture of some opposing opinions is also evidence that a complete picture of the current literature was obtained through the search.

Conclusion

Cognitive and neuropsychological impairments experienced post-treatment by pediatric brain tumour survivors almost always manifest themselves as difficulties with sustaining attention, and very often as limitations in short-term or working memory, a slower cognitive processing speed, and deficits in executive functioning. Multiple statistical analyses reveal that the effect of brain tumour treatment in childhood on these cognitive skills is very strong, and causes decline in anywhere from 35& to 85% of individuals. Impairment may progress over periods of time as long as 10 years depending on the cognitive domain in question, but strong conclusions based on study results could not be made in this regard.