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Cognitive Profiles in Children Treated for Brain Malignancies as Compared to Children with Traumatic Brain Injuries

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Abstract

Objective: We investigated the cognitive profiles of children treated for brain tumours as compared to children treated for brain traumas. Furthermore how various moderators such as age at the time of injury/diagnosis, time since injury/ diagnosis, and severity of the injury might correlate with outcome.

Methods: 64 children treated for brain tumours and 77 with traumatic brain injures (6-18 yrs) who were all assessed with cognitive tests between 2000 and 2009 were investigated.

Results: There were no significant difference between the two diagnostic groups on total IQ, verbal comprehension, perceptual organization, processing speed and freedom of distractibility or verbal working memory. Moreover, no significant difference between, the children with brain tumours, who had undergone cranial radiation therapy and those who had not.

Conclusions: Findings indicate that all children who have been treated for brain tumours independent of treatment should be screened with cognitive measures and followed over time.

Keywords: Children; Cognitive profiles; Traumatic brain injury; Brain malignancies

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Introduction

Paediatric oncology has during the last decades been very successful in treating childhood cancer. Neurosurgery, in combination with Cranial Radiotherapy (CRT) and or chemotherapy, is the treatment modalities that are available for children with malignant brain tumours. However, this treatment is not free from complications. Common medical problems are neurological [1], endocrinological [2] or oncological [3]. Moreover there is also a significant risk of neuro-cognitive sequelae [4]. This risk is highest for those children that have got both CRT and chemotherapy although children that just have been operated or just have got chemotherapy seem also at risk [5,6]. Deficits in cognitive processing skills are also commonly observed in the long-term follow-up of children with other aetiologies to the acquired brain injury. Deficits in attention, memory, executive functions and speed of information processing are reported to be the most common cognitive problems [7]. If these cognitive deficits are present during development they impede learning and the acquisition of new skills and knowledge, resulting in the global cognitive dysfunction commonly observed in the long-term follow-up of children with acquired brain injuries [8]. Clinical evaluations and observations of the cognitive consequences after acquired brain injuries in childhood indicate that there may be differences in cognitive consequences depending on the character of the injury. In order to develop specific interventions for children with neuro-cognitive consequences after acquired brain injuries it seems crucial to investigate these possible differences in cognitive style dependant on the aetiology of the injury. The aim of the present study was therefore to investigate and compare the cognitive profiles in children treated for brain tumours as compared to children with a Traumatic Brain Injury (TBI).

Materials and Methods

The paper presents an investigation of a clinical sample, and is based on historical data from neurocognitive examinations during ten years in a Neuropediatric unit at a children´s hospital in Sweden.

Table 1: Descriptive data for the two study groups.

	Brain tumour, n (%)	TBI, n (%)
Total n	66	74
Girls/ Boys	35/31 (53%/47%)	26/48 (35%/65%)
Aetiology of the brain injury		
Traffic accident	(n.a.)	37 (50%)
Falling accident	(n.a.)	12 (16%)
Violence	(n.a.)	2 (3%)
Sports accident	(n.a.)	11 (15%)
Other TBI	(n.a.)	12 (16%)
Low-grade astrocytoma	26 (39%)	(n.a.)
Medulloblastoma and PNET	18 (27%)	(n.a.)
Craniopharyngeoma	7 (11%)	(n.a.)
Other brain tumour	15 (23%)	(n.a.)
GCS[a] <8 at initial arrival in hospital	(n.a.)	27 (36%)
Radiation therapy	40 (61%)	(n.a.)
Medical late effects at the time for the neurocognitive testing		
Epilepsy	5 (8%)	1 (1%)
Endocrine complication	24 (36%)	2 (3%)
Visual impairment	30 (46%)	15 (20%)
Hearing impairment	13 (20%)	5 (7%)
Motor deficiency	10 (15%)	19 (26%)
Language deficiency	3 (4%)	4 (5%)
	mean (SD); range	mean (SD); range
Age at head trauma/tumour diagnosis, years	7.5 (3.4); 0-15.6	12.0 (3.2); 3.5-16.3
Time elapsed from tumour diagnosis/head trauma to neurocognitive testing, years	4.9 (3.4); 0-15.1	2.6 (2.7); 0-11.8
Age at neurocognitive testing	12.4 (2.8); 6-18	14.5 (1.9); 10-19
[a]GCS = Glasgow Coma Scale		

Participants

The sample included children treated for malignant brain tumours and children with TBI, who were followed at the Neuropediatric and the Oncology Units at Astrid Lindgren Children's Hospital Stockholm during the period 2000 - 2009. The criterion for inclusion was an investigation with cognitive tests including a complete WISC (Wechsler Intelligence Scales for Children) protocol. Annually, about 20-25 children are diagnosed with brain tumours at Astrid Lindgren Children's Hospital in the Stockholm region and 120 children are yearly referred to the Neuropediatric rehabilitation unit after TBI. In 2006 the hospital developed a long term neurorehabilitation program where approximately 75% of the children with brain tumours are referred to neuro-cognitive examination after the cancer treatment has been completed. About 50 children/year with TBI are referred to neuro-cognitive investigation. Before the year 2006 children both with brain tumours as well as TBI were investigated to a lesser extent. The neuro-cognitive investigation normally contains the WISC for testing general cognitive level of children of 7-18 years of age. However, complete WISC protocols are not available for children with too poor functions or those who were not cooperating, i.e. those who could not or would not complete the test. In total, data from 66 children who had been treated for brain tumours, and 74 children with traumatic brain injuries were included in the study. Descriptive data for the two groups are presented in Table 1. The brain tumour group involved patients diagnosed between 1992 and 2007. The children with TBI were injured between 1993 and 2008.

Assessments

Cognitive functions: The general intellectual ability of the children was assessed employing the Wechsler Intelligence Scales for Children (WISC-III, WISC IV), with a mean of 100 and SD of 15 [9]. Factor analyses were estimated from the WISC-III/WISC IV on Verbal Comprehension, Perceptual Organization, Freedom of Distractibility (attention), and Speed of Processing.

Memory: In the 15 word test [10], assessing verbal memory, the children had to listen to simple unrelated words presented 5 times. The task was after each presentation to repeat as many words as possible by free recall. In addition, the total number of words remembered in connection with delayed free recall 40 minutes later was scored separately. In accordance with the Rey-Osterrieth Complex Figure

Table 2: Mean, standard deviation and range for neuro-cognitive tests of children with brain tumours and children with TBI.

	Brain tumour, n (%)	TBI, n (%)
Total n	66	74
Girls/ Boys	35/31 (53%/47%)	26/48 (35%/65%)
Aetiology of the brain injury		
Traffic accident	(n.a.)	37 (50%)
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Hearing impairment	13 (20%)	5 (7%)
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Age at head trauma/tumour diagnosis, years	7.5 (3.4); 0-15.6	12.0 (3.2); 3.5-16.3
Time elapsed from tumour diagnosis/ head trauma to neurocognitive testing, years	4.9 (3.4); 0-15.1	2.6 (2.7); 0-11.8
Age at neurocognitive testing	12.4 (2.8); 6-18	14.5 (1.9); 10-19
[a]GCS= Glasgow Coma Scale		

Recall [10], which is a measure of visuo-spatial memory, the children were asked to reproduce a complex geometrical design 30 minutes after having copied it and without knowing in advance that they would be requested to do this. The accuracy score is the number of elements remembered and reflects the amount of information retained for this period of time.

Severity of the brain injury: A rough estimation of the potential severity of the brain injury, with respect to possible neuro-cognitive deficits, was obtained. Considering the adverse effect of radiation against the developing brain, children who had received CRT as part of their brain tumour treatment were assigned to the *severe injury* group. According to the approach generally used for estimating the severity of TBI, children with a Glascow Coma Scale (GCS) score of <8 at initial arrival to the hospital were considered having a *severe injury*.

Procedure

Data for the most recent test performance of each child were collected from the medical records, together with medical and demographic data. The study was approved by the Ethical Committee at Karolinska Institutet.

Statistical analyses

In order to analyze the differences in neuro-cognitive test scores between brain tumour survivors and children with TBI at a group level, t-test were performed. Moreover, post-hoc ANOVA was used to examine any differences in test scores between all four sub groups: the children with more or with less severe injury due to brain tumour or TBI, respectively. Bonferroni correction was applied to avoid type-1 errors due to multiple tests in the ANOVA. Chi^2 calculations were used to compare brain tumour survivors and children with TBI as regards the frequency of children performing significantly below average for age. Similarly, the frequency of scores significantly below average for age was analyzed in relation to severity of the brain injury using Chi^2 tests. Finally, the association between cognitive outcome and the variables age at the time of injury, and time since injury/

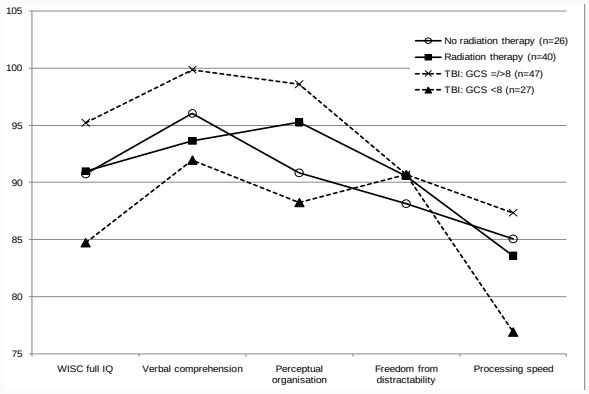

Figure 1: Cognitive profiles in the four groups measured as IQ scores (mean =100; SD =15).

cancer diagnosis was analysed with Pearson correlation, 2-tailed.

Results

Descriptive statistics

The two study groups differed significantly with respect to age at the time of injury/tumour diagnosis, with the children with TBI typically being older than the children who were diagnosed with a brain tumour (t=-7.8, p <.001; Table 1). Moreover, the time elapsed from diagnosis/injury to the neurocognitive testing was significantly longer in the oncology group (t=5.1, p <.001). Consequently, the child's age at testing differed in the same direction (t=5.1, p <.001).

Brain tumour and TBI: Neurocognitive outcome

No statistically significant differences were found in neurocognitive test outcomes between brain tumour survivors and children with TBI (Table 2).

Difference from average for age

At a group level, the scores for *full scale IQ* as well as the four indices of WISC were slightly below average for age for both brain tumour survivors and children with TBI, with the Processing speed factor demonstrating the largest difference from average for age for both groups. Subsequently, the frequency of test results significantly below the average for age was examined. Forty four per cent of the children who had been treated for brain tumours, and 34% of the children with TBI had a Full scale IQ below average, indicating general neurocognitive difficulties.

Severity of the brain injury: Neurocognitive outcome

Subsequently analyses were made of the *severity groups* of brain tumour (radiation therapy or no radiation therapy) and TBI (GCS <8 or >/=8 at the initial arrival at the hospital). Test outcomes are presented in Table 3. Comparisons of the WISC *full scale IQ* and indices and the 15 Words verbal memory between all four *severity groups* rendered a few statistically significant differences (post-hoc ANOVA with Bonferroni correction): the children with GCS <8 at arrival had lower scores than those with GCS >/=8 regarding *full scale IQ* (mean difference=12.8, p <0.05) and *perceptual organisation* (mean difference=12.8, p <0.05). Moreover, the four *severity groups* displayed fairly similar profiles, with *processing speed* as the main difficulty (Figure 1).

Difference from average for age

The frequencies of radiated and non-radiated brain tumour survivors with markedly poor neuro-cognitive outcome (test scores significantly lower than average for age) are presented in Table 3. A further exploration of the neurocognitive outcome of children who had or had not received radiation revealed no statistically significant differences. In addition to WISC scores, verbal and visuo-spatial memory outcome is presented (Table 3).

Table 3: Brain tumour survivors with neurocognitive outcome significantly lower than average for age, in relation to cranial radiation therapy (CRT).

	1 SD or more below average for age; % (n)	
	No CRT	CRT
WISC Full scale IQ	40.7% (11)	46.2% (18)
WISC Verbal comprehension	29.6% (8)	41.0% (16)
WISC Perceptual organisation	37.0% (10)	20.5% (8)
WISC Freedom from distractibility	44.4% (12)	48.7% (19)
WISC Processing speed	59.3% (16)	48.7% (19)
15 words immediate recall [a]	27.3% (6)	12.1% (4)
15 words delayed recall [a]	27.3% (6)	12.1% (4)
ROCF copy [b]	22.7% (5)	25.0% (4)
ROCF delayed recall [c]	65.2% (15)	61.1% (11)

[a]Missing data for the 15 Words Verbal Memory test: 4 children not treated with CRT, and 7 children treated with CRT.
[b]Missing data for the ROCF copy test: 5 children not treated with CRT, and 11 children treated with CRT.
[c]Missing data for the ROCF delayed recall test: 4 children not treated with CRT, and 9 children treated with CRT.

Time since injury/brain tumour diagnosis

Time elapsed since diagnosis of the brain tumour was correlated to WISC Full scale IQ (r=-.36, p <.01) and the indices Verbal comprehension (r=-.35, p <.05) and Processing speed (r=-.35, p <.05), indicating a poorer performance in children a longer time since diagnosis. Among the children with TBI, there were no associations between time elapsed since the head trauma and neuro-cognitive outcome.

Age at injury

The child's age at brain tumour diagnosis or head trauma, respectively, was not systematically associated with test scores (Pearson's correlation).

Discussion

The comparison of neuro-cognitive profiles between children who had been treated for brain tumours and children with TBI revealed no significant differences. Also when the groups were divided into severity groups no statistical difference was found between children surviving brain tumour and children with TBI. However, children treated with CRT and children with GCS <8 showed cognitive results with a group mean more than one standard deviation below average for age indicating general neurocognitive difficulties with slow speed of processing and attentional difficulties as the most noticeable dysfunctions. These data supports earlier findings [11]. The essential finding in the present study was instead that no significant difference was found between children with brain tumours treated with CRT and those who were not. This applied to cognitive level, verbal comprehension factor, perceptual organization, processing speed, and freedom of distractibility as well as verbal and visuospatial memory. Both groups showed results below average for age on all these measures. This contrasts previous research suggesting that the

most adverse effects are to be seen in patients who have undergone CRT [5]. These deficits have mainly been attributed to the effects of CRT, but there is increasing recognition that tumour infiltration, surgical resection and chemotherapy likely play a role in the cognitive outcome of brain tumour patients [12]. The present results indicate that surviving a brain tumour, independently of treatment, implies a risk of overall decline in intellectual functioning with processing speed and attentional factors being most affected. The children in the brain tumour group indicated a decline in neurocognitive performance the longer time had passed since diagnosis. This cognitive decline is earlier reported in the literature and indicates that aside from declines in intellectual and academic achievements a sequence of deterioration is found beginning less than 6 months following treatment. This consists of 1) initial deterioration in memory and attention skills 2) then perceptual disturbances of visual spatial organization and sequencing of actions, 3) a decline in analysis, synthesis and abstract thought and eventually 4) a decreased vocabulary [11]. The child's age at brain tumour diagnosis or head trauma, respectively, was in this retrospective study not systematically associated with test scores, possibly due to small groups and heterogeneity. This result is in contrast to several studies, where young age at injury has been found to negatively influence outcome following traumatic brain injury [13], as well as children treated for brain tumours [5,14]. The clinical characteristic of the present study sample is a limitation that prevents us from drawing reliable conclusions. We have reason to suspect that the children were not systematically recruited to the sample. For example, all children who had undergone CRT at the hospital are referred to neuro-cognitive follow-up. On the other hand, of the non-radiated children only those with obvious problems used to be referred. Yet, it can be argued that less obvious problems may be overseen among these children, if we remain focusing on children with cranial radiation only. Preventing these late effects on cognitive processing is a challenge for both the medical team and for psychologists and rehabilitation specialists. Prevention depends in part on the ability to predict those at greatest risk. Advances in neuroimaging hold promise for helping to predict during the acute phase of treatment those patients who may suffer the greatest neuro-cognitive declines. Consequently these patients may have risk-adapted therapy that seeks to lessen morbidity. For survivors who show neuro-cognitive decline following cancer treatment, rehabilitation similar to that used for children with TBI have shown some effectiveness [15-17]. For newly diagnosed patients who are identified as being at risk prophylactic interventions such as cognitive training may offer the best hope of preventing late effects. There is a great need for long term follow-up programs for children treated for brain tumours. These follow up programs ought to include not only medical aspects but also neuro-cognitive and psychological late effects. In order to be able to recommend treatment and pedagogic interventions we suggest a model where all children who have been treated for brain tumours independent of treatment at an early stage should be screened with cognitive measures and at key ages followed over time.

In conclusion, in spite of the methodological shortcomings of the study, the findings are intriguing and encourage well designed prospective studies in larger groups appear to be required in order to assess possible differences in cognitive deficits between children with different aetiologies to an acquired brain injury.

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