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Cognitive Dysfunction in Children With Brain Tumors at Diagnosis

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Background. Survivors of brain tumors have a high risk for a wide range of cognitive problems. These dysfunctions are caused by the lesion itself and its surgical removal, as well as subsequent treatments (chemo- and/or radiation therapy). Multiple recent studies have indicated that children with brain tumors (BT) might already exhibit cognitive problems at diagnosis, i.e., before the start of any medical treatment. The aim of the present study was to investigate the baseline neuropsychological profile in children with BT compared to children with an oncological diagnosis not involving the central nervous system (CNS). ***Methods.*** Twenty children with BT and 27 children with an oncological disease without involvement of the CNS (age range: 6.1–16.9 years) were evaluated with an extensive battery of neuropsychological tests tailored to the patient's age. Furthermore, the child and his/her parent(s) completed self-report questionnaires about emotional functioning and quality of life. In both groups, tests were administered before any therapeutic intervention such as surgery, chemotherapy, or irradiation. Groups were comparable with regard to age, gender, and socioeconomic status. ***Results.*** Compared to the control group, patients with BTs performed significantly worse in tests of working memory, verbal memory, and attention (*effect sizes* between 0.28 and 0.47). In contrast, the areas of perceptual reasoning, processing speed, and verbal comprehension were preserved at the time of measurement. ***Conclusion.*** Our results highlight the need for cognitive interventions early in the treatment process in order to minimize or prevent academic difficulties as patients return to school. Pediatr Blood Cancer 2015;62:1805–1812.

Key words: at diagnosis; attention; cognitive problems; memory; pediatric brain tumor

INTRODUCTION

Although cancer remains the current leading cause of death by disease in children under 15 years, recent advances in pediatric cancer treatment have significantly increased long-term survival rates up to 80%.[1] However, potentially serious treatment complications as well as sensory deficits such as hearing loss after chemotherapy, optic atrophy from cranial radiation therapy, or increased intracranial pressure are recognized in the literature.[2] Patients with brain tumors (BT) are especially prone to neurocognitive sequelae, which may result from the tumor itself or potentially from various therapeutic interventions such as surgery, radio- and chemotherapy.[1] Long-term follow-up studies of children with BT have demonstrated a range of cognitive deficits, affecting intelligence, memory, attention, executive function, and academic performance.[e.g., 3,4] Poor academic achievement is likely to negatively influence the patients' chances of reaching subsequent vocational and economic goals.[5]

However, cognitive impairment caused by a tumor can be highly variable[6] and some deficits might not become evident until several years after treatment.[7] Shortman and colleagues[8] reported that pediatric patients with BT showed significantly reduced performance on measures of processing speed, memory, and attention when compared with healthy age-matched children after surgery. The adverse effects of radiation on the developing brain have long been recognized.[9,10] Impairment of learning and memory is among the most common sequelae of radiotherapy.[11] Chemotherapy is usually less neurotoxic than radiation, but can also negatively affect neurocognitive functions including attention, processing speed, executive functioning, and memory.[12,13]

The majority of pediatric brain tumor studies have focused on the post-treatment cognitive deficits in children with brain tumors. Presurgery assessments are often not undertaken due to the associated practical difficulties.[8] Therefore, literature on the pre-treatment neuropsychological status of these patients is scarce. Lazareff and Castro-Sierra[14] reported that children with cerebellar tumors, who were tested 3–4 days prior to surgery, performed worse on measures of auditory memory than the age-matched healthy control group, which consisted of patients' siblings, while their visual memory performance was comparable. Varela and colleagues[15] investigated the cognitive profile of posterior cerebellar and fourth ventricle tumors in 24 children (range 4–15 years) before any therapeutic intervention and compared their performance with age-matched children treated in the same hospital for abdominal ailments. No group differences were found in measures of IQ, visual perception, visual memory, and visuomotor integration skills. Attention, verbal learning, and memory were not measured in this study.

Di Rocco and colleagues[16] investigated cognitive functioning in children with medulloblastoma and astrocytoma before surgery (41 children, age range 2–6 years). They showed that in some children attention and executive problems were already present before treatment. Similarly, Iuvone and colleagues[17] reported that prior to any medical treatment, almost 50% of 83 children (age range 7 months to 16 years) with various BT showed difficulties in some cognitive domains such as attention, verbal working memory,

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planning tasks, and visual-motor integration. Twelve percent of these children reached IQ values below the normal range, while 6% displayed values in the range of mental retardation. Stargatt and colleagues[18] showed that children aged 4–16 with posterior fossa tumors showed deficits in sustained attention and processing speed even before surgery, and that these deficits increased over time during the three subsequent years after surgery and cranial radiation. Even though these three studies[16–18] showed that impairments of some basic functions like attention and memory can be detected at diagnosis, none of the studies included a control group of children newly diagnosed with a non-CNS oncological disease (CG).

In summary, a number of empirical studies indicate that specific functional deficits in children with BT can be measured before surgical or subsequent treatments commence. Cognitive functions like memory and attention, which are key functions for acquiring new information, seem to be affected most.[13] The CNS is constantly developing in childhood, and therefore interruption of this process by tumor infiltration can profoundly impair the creation of new neural networks and in consequence, cognitive development. The present study investigated the cognitive performance of children with newly diagnosed BTs in comparison to age-matched patients with other oncological diseases without involvement of the CNS. Since anxiety, apprehension, and physical discomfort are likely to affect cognitive functioning, it would be relevant to compare the performance of both groups of children. Children in our oncological CG are, due to their illness, exposed to a similar level of emotional and physical distress, but are not expected to show systematic cognitive problems.

Given that others have already reported on cognitive problems in children with BT at diagnosis,[16–18] we hypothesized that children with BT would perform poorer in tests of attention and memory as compared to CG patients. Furthermore, we postulated that the number of test scorings below one standard deviation or more below the age-adjusted normative mean would be higher in the BT sample than in the CG.

METHODS

In January 2010, a neuropsychological care program was implemented in the medical treatment routine at the Department of Pediatric Hematology/Oncology of the Children's University Hospital in Bern. All children aged 3–18 years suffering from an oncological disease, with or without involvement of the CNS, have been included in this clinical routine. Patients usually complete three standardized cognitive test batteries tailored to their age to monitor the cognitive development: (1) at diagnosis (baseline assessment), (2) immediately after the intensive medical treatment phase (i.e., in children with acute lymphoblastic leukemia at the beginning of maintenance therapy), and (3) 1 year after the end of treatment. The test battery for baseline testing covers the neuropsychological domains at greatest risk following treatments like radiation and/or chemotherapy, such as attention, working memory, processing speed, visuospatial abilities, learning, and memory.[19] If cognitive impairments are detected, cognitive rehabilitation programs are introduced immediately with the goal to minimize or even prevent long-term sequelae. For the present exploratory study, baseline data have been analyzed (2010–2013). The study has been approved by the Cantonal Ethics Committee of Bern and followed the principles outlined in "World Medical Association Declaration of Helsinki: Research involving human subjects".

Participants

Of the children who underwent neuropsychological testing between 2010 and 2013, 47 children met the following inclusion criteria for the present study: (1) age between 6 and 17 years at diagnosis to ensure comparability of the age-tailored tests (2) no premorbid neurological or psychiatric history (3) in the case of sensory deficits: not interfering with the neuropsychological testing process (4) at least 13 of 16 cognitive measures completed (see below), and (5) IQ $\geq$ 70. Children with brain stem tumors were excluded from neuropsychological assessment due to their poor prognosis. Patients with tuberous sclerosis complex and neurofibromatosis type one were excluded from the study due to their potential secondary cognitive problems not directly related to the tumors. To test for CNS involvement in children with leukemia and lymphoma, cerebrospinal fluid was tested for malignant cells. In patients with any neurological abnormality, an MRI was performed to exclude CNS metastases, which were not found in any of the children. All tested children had IQs above 70. Therefore, no child had to be excluded for reasons of intellectual disability. In total, 20 children with BT and 27 control children (CG) with non-CNS cancer (nine children with acute lymphoblastic leukemia, five children with Hodgkin lymphoma, four children with osteosarcoma, three children with Ewing sarcoma, two children with lymphoma, two children with acute myeloid leukemia, one child with rhabdomyosarcoma, and one child with paraganglioma) were included in the analyses. Diagnostic characteristics of the children with BT are shown in Table II. Neuropsychological assessments with children of both groups were performed shortly after diagnosis and before therapeutic intervention (e.g., surgery, irradiation, chemotherapy). The demographic characteristics of both groups BT and CG are presented in Table I. Diagnostic characteristics of the children with BT are shown in Table II.

Cognitive Assessments and Questionnaires

An extensive cognitive test battery was performed in both groups of children. All tests were applied in a randomized order. German versions and German reference norms were used. Because no German reference norms are available for the CMS Stories, we used the American norms, which have been verified in many years of clinical experience. Raw scores were transformed into standardized IQ scores, index scores, or percentiles adapted to the age, as dictated by the respective test manuals. Impairment was defined as a performance of one standard deviation below the normative mean (i.e., IQ scores/index score $<$85; percentile $<$16 or $>$84, depending on the respective test). For all neuropsychological functions of interest (intelligence, verbal learning and memory and attention), two different tests were administered to increase the confidence in the validity of the measurement results.

Intelligence. General intelligence (Full Scale IQ, FSIQ) was assessed using the German version of the "Wechsler Intelligence scale for children" (WISC).[20,21] Additionally, nonverbal intelligence was measured using the Test of Nonverbal Intelligence, Third Edition (TONI-3).[22]

Perceptual reasoning. The perceptual reasoning index score of the WISC-IV (subtests block design, picture concepts, and matrix reasoning) was used for perceptual reasoning.

TABLE I. Demographic Characteristics of Brain Tumor Patients and Oncological Control Patients

Variable		Measure	Group	
			Brain tumor patients	Control patients
Age at diagnosis	Months	M (SD)	128 (39)	147 (36)
		Range	75–186	73–198
Gender	Girls	n (%)	7 (35.0)	14 (55.6)
Parental education[a]	Vocational training	n (%)	12 (60.0)	14 (51.9)
	Secondary school	n (%)	1 (5.0)	2 (7.4)
	University	n (%)	3 (15.0)	5 (18.5)
	Not specified	n (%)	4 (20.0)	6 (22.2)

M, mean; SD, standard deviation; n, sample size. [a]Parental education serves as a proxy for socioeconomic status (SES).

Verbal comprehension. Verbal comprehension was assessed using the verbal comprehension index score of the WISC-IV (subtests similarities, vocabulary, and comprehension).

Working memory. The working memory index score of the WISC-IV (subtests digit span and letter-number sequencing) was used for working memory.

Processing speed. Processing speed was measured using the subtest symbol search of the WISC-IV. This subtest requires less fine-motor accuracy than the second subtest of the WISC-IV (coding) and, therefore, allows testing bedside and/or while wearing an arm splint on the forearm of the dominant hand.

Verbal learning and memory. Two different verbal tests were used to assess verbal learning and memory: the German version of the "Rey Auditory Verbal Learning Test" (RAVLT)[23] and the subtest "stories" from the Children's Memory Scale (CMS).[24]

Sustained attention. The computerized "Conner's Continuous Performance Test" was applied to assess selective and sustained attention performance (CPT-II version 5),[25] which was measured in terms of inattention (omission errors) and impulsivity (commission errors).

Divided attention. The subtest "Divided Attention" of the computerized "Test of Attention Performance" (TAP version 2.2).[26] was used to assess divided attention performance. Performance was measured in terms of inattention (omission errors) and impulsivity (commission errors) in both visual and auditory tasks.

Questionnaires. Two questionnaires were filled out by the participating children and their parents: The Strengths and Difficulties Questionnaire (SDQ)[27] and the quality of life inventory (Inventar zur Erfassung der Lebensqualität von Kindern und Jugendlichen, ILK).[28]

Procedure

Bedside neuropsychological testing was performed, the physical and emotional well-being of the children permitting. Children were tested in a quiet environment and in a one-to-one setting by a trained neuropsychologist. Regular breaks were offered.

Statistical Analyses

Due to small sample sizes (20 children with BT, 27 CG children), non-parametric statistical tests were performed. One-tailed Mann–Whitney *U*-tests were used to compare the scores of each test and subtest between children with BT and CG patients. A *P*-value <0.05 was considered a significant effect. Furthermore, effect sizes of group differences between children with BT and CG children were calculated. Effect sizes complement inferential statistics (e.g., *P*-values) by examining the strength of group differences independent of sample size. Effect sizes were calculated with the formula $\Phi = Z/\sqrt{N}$.[29] A Φ-coefficient near 0.5 indicates a large difference between groups (large effect size), a coefficient near 0.3 indicates a medium effect size, while a Φ near to 0.1 indicates a small difference between groups (small effect size). Additionally, it was analyzed if frequencies of impairment (i.e. performances at least one standard deviation below the normative mean) were higher in children with BT than CG children by means of one-tailed Pearson's χ^2. All analyses were performed using the Statistical Package for Social Sciences software for Windows, version 20 IBM SPSS Statistics (Chicago, Illinois, 2011).

RESULTS

Analyses of Demographic Data

Table I provides the patients' demographic details. BT and CG children were comparable in age at assessment ($U = 344.5$, $P = 0.11$), the distribution of gender ($\chi^2(1) = 1.95$, $P = 0.24$) and country of origin ($\chi^2(5) = 5.33$, $P = 0.38$). Parental education was examined as a proxy for socioeconomic status (SES). No statistically significant differences were found in the professional status of the parents between children with BT and the CG children ($\chi^2(3) = 0.35$, $P = 0.95$).

Analyses of Group Differences in Cognitive Performance

Results are summarized in Table III. Compared to CG children, children with BT performed significantly worse on measures of verbal working memory, verbal learning and delayed verbal recall, recognition of words and stories and attention (commission errors in sustained and divided attention). There was a tendency for the WISC Full-Scale-IQ to be lower in BT patients; this however did not reach statistical significance. No significant differences between children with BT and CG children in measures of verbal comprehension ($P = 0.48$), perceptual reasoning ($P = 0.08$), and in the omission error rates of the sustained ($P = 0.36$) and divided attention tasks ($P = 0.12$) were found.

Effect sizes (phi-coefficient) revealed a medium-to-large group difference in processing speed ($\Phi = 0.35$), verbal learning ($\Phi = 0.41$) and verbal recall of words ($\Phi = 0.33$) and stories

TABLE II. Diagnostic Characteristics of the Brain Tumor Patients

No.	Histology[a]	Location[b]	Brain stem involvement	Symptoms	Symptom duration	Neurological deficits[c]	Ataxia	Oculomotor palsy	Epileptic seizures	Hydrocephalus[d]
1	MB	IT	NO	Nausea/vomiting Headaches	<100 days	No	No	No	No	Moderate
2	ONG[e]	SU	No	Impaired hearing Impaired vision Fine-motor problems	≥100 days	Yes	No	No	No	No
3	NGCT	SM	No	Nausea/vomiting	<100 days	Yes	No	Yes	No	Marked
4	PA	SH	No	Headaches Fatigue Vestibular disorder Limping (right) Back pain	<100 days	Yes	Yes	No	No	Marked
5	NGCT	SU	No	Nausea/vomiting Headaches	<100 days	No	No	No	No	No
6	PNET	SH	No	Hemiparesis right	<100 days	Yes	No	No	No	No
7	ODG	SH	No	Nausea/vomiting Strabismus Abdominal pain	<100 days	No	No	No	No	No
8	DNT	SH	No	Headaches Fatigue	<100 days	No	No	No	Yes	No
9	PA	SM	No	Nausea/vomiting Headaches Impaired vision Slurred speech Paraesthesias	<100 days	Yes	No	No	No	Marked
10	CP	SM	No	Impaired vision	≥100 days	No	No	No	No	No
11	PA	IT	No	Nausea/vomiting Headaches Impaired vision Loss of appetite	<100 days	No	No	No	No	Moderate
12	NGCT	SM	No	Nausea/vomiting	<100 days	No	No	no	No	No
13	PA	IT	No	Nausea/vomiting Headaches	≥100 days	Yes	Yes	no	No	No
14	CPT	SH	No	Nausea/vomiting Fatigue	<100 days	No	No	no	No	No
15	CS	SH	No	Nausea/vomiting Headaches	≥100 days	Yes	Yes	no	No	No
16	Unknown	SM	No	Headaches Fatigue	≥100 days	No	No	no	No	No
17	MB	IT	No	Nausea/vomiting Headaches	<100 days	No	No	no	No	Marked
18	GE	SM & IT	No	Nausea/vomiting Headaches	>100 days	No	No	yes	No	Marked
19	PA	SH	No	Nausea/vomiting Headaches	<100 days	No	No	no	No	Marked
20	PA	SM	No	Headaches	<100 days	No	No	no	No	No

[a]Histology: CS, chondrosarcoma; CP, craniopharyngioma; CPT, choroid plexus tumor; DNT, dysembrioplastic neuroepithelial tumor; GE, germinoma; MB, medulloblastoma; NGCT, nongerminomatous germ cell tumor; ODG, oligodenodroglioma; ONG, optic nerve glioma; PA, pilocytic astrocytoma. [b]Location: IT, infratentorial; SH, supratentorial hemispheric; SM, supratentorial midline; SU, supratentorial unspecified. [c]Neurological deficits (manifested as slight motor weakness, clumsiness or impairments in coordination and reflexes): no, absent; yes, mild, not interfering with daily life. [d]Hydrocephalus: no, absent; moderate, supratentorial convexity spaces not completely effaced; marked, supratentorial convexity spaces completely effaced. [e]History of neonatal meningitis.

TABLE III. Analyses of Group Differences in Cognitive Performance Between Brain Tumor Patients and Oncological Control Patients on Standardized Measures

		Group						Test statistics		
		Brain tumor patients (n = 20)			Control patients (n = 27)			Group comparisons		Effect sizes
Function	Measure	n	Median	Range	n	Median	Range	U[c]	*P*	Φ (Phi)
Fluid intelligence (TONI-3)[a]	Nonverbal IQ	17	100	89–130	24	100	83–150	243.5	0.15	0.15
Intelligence (WISC-IV)[a]	Full scale IQ	20	99	77–117	27	108	67–132	339.0	0.051	0.26
	Verbal comprehension (*WISC Index*)	20	100	81–126	27	101	67–126	272.5	0.48	0.01
	Perceptual reasoning (*WISC Index*)	20	99	73–121	27	106	73–141	336.5	0.08	0.21
	Working memory (*WISC Index*)	20	95	80–108	27	102	71–141	385.0	0.03*	0.28
	Processing speed (*WISC Index*)	19	97	62–123	26	103	74–134	308.0	0.14	0.16
Verbal learning (RAVLT)[a]	Learning (*PR trial* 1–5)	19	10	1–99	26	70	10–99	371.0	<0.01** (+)	0.41
	Recall (*PR trial* 7)	19	14	1–99	26	69	1–99	330.5	0.01**	0.33
	Recognition (*PR*)	19	53	1–88	26	75	5–88	312.0	0.03*	0.27
Verbal learning[a]	Immediate recall (*PR*)	14	50	2–95	22	75	2–99	211.5	0.03*	0.27
(CMS Stories)[a]	Delayed recall (*PR*)	14	44	2–99	22	80	2–99	218.0	<0.01** (+)	0.30
	Delayed recognition (*PR*)	14	50	2–84	22	75	16–98	226.0	<0.001*** (++)	0.47
Sustained attention (CPT-II)[b]	Commission errors (*PR*)	20	65	3–89	26	18	1–94	156.0	0.01**	0.34
	Omission errors (*PR*)	20	38	21–99	26	36	20–96	244.0	0.36	0.27
Divided attention (TAP)[a]	Commission errors (*PR*)	17	22	2–100	27	79	4–100	322.0	0.03*	0.34
	Omission errors (*PR*)	17	29	1–100	27	46	1–96	293.5	0.12	0.05

Significance level: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P = <0.001$ (uncorrected); (+ = $P < 0.05$; ++ = $P < 0.01$ after Holm–Bonferroni-Correction). [a]High values indicate good performance. [b]Low values indicate good performance. [c]Mann–Whitney *U*-test. PR, percentile rank.

(Φ = 0.47) as well as in the commission error rates of both divided (Φ = 0.34) and sustained (Φ = 0.34) attention tasks. All other effect sizes were small-to-negligible (Φ = 0.05–0.28).

Analyses of Frequencies of Impairment in Cognitive Performance

Results are shown in Table IV. Children with BT had higher frequencies of impairment compared to CG children in verbal learning and recall as well as in the commission error rates of the divided attention task (more children in the group of BT patients performed one *SD* or more below the normative mean as compared to the children of the CG). There were no differences in frequencies of impairment in BT and CG children concerning WISC-IV Full-Scale-IQ and nonverbal IQ, verbal comprehension, perceptual reasoning, working memory, processing speed, verbal recognition, the commission error rates in the sustained attention, and the omission error rates in the sustained and the divided attention tasks. Four children with BT (20%) showed a performance of one standard deviation below the normative mean in at least four different measures (intelligence, working memory, verbal learning, and attention) compared to one control child (4%).

Analyses of Group Differences in Emotional Functioning and Quality of Life

All quality of life measures for both patient groups and their parents were in the range between percentiles 70 and 100, indicating non-pathological findings. Concerning overall stress values (measured by SDQ), 95% of the children with BT and 100% of the CG children indicated average stress levels, while one child in the BT group revealed an elevated stress level. No group differences were found in the self-reported questionnaires regarding quality of life and emotional stress. The quality of life for children of the two groups ($\chi^2(9) = 9.00$, $P = 0.44$) and their parents ($\chi^2(11) = 12.71$, $P = 0.31$) and the overall stress score for children ($\chi^2(2) = 3.73$, $P = 0.15$) and their parents ($\chi^2(2) = 2.36$, $P = 0.31$) were not significantly different.

DISCUSSION

We investigated a variety of cognitive functions in children with a newly diagnosed oncological disease with or without CNS involvement before any major therapeutic intervention. Results revealed significant differences between the respective groups' performances in the areas of verbal learning, attention, and working memory to the disadvantage of children with BT.

In our two different attention tasks (TAP and CPT), children with BT committed more errors of commission than the CG, reflecting an impulsive response style. Several studies have reported attentional deficits in children with BT,[17,18,30,31] although most findings hint at inattention problems rather than impulsivity. One explanation for the discrepancy in results may lie in the different nature of the measures analyzed: Most studies used a composite measure of attention [e.g., 8,16,32,33] or have

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TABLE IV. Analyses of Frequencies of Impairment in Brain Tumor Patients and Oncological Control Patients

		Group		Test statistic	
		Brain tumor patients	Control patients		
Function	Measure	<1SD n (%)	<1SD n (%)	χ^2	Fisher's exact test (*P* one tailed)
Fluid intelligence (TONI)[a]	Nonverbal IQ	2 (12.0)	2 (8.0)	0.13	0.55
Intelligence (WISC-IV)[a]	Full scale IQ	6 (31.6)	4 (15.4)	1.67	0.18
	Verbal comprehension (*WISC Index*)	1 (5.0)	5 (18.5)	1.89	0.18
	Perceptual reasoning (*WISC Index*)	3 (15.0)	3 (11.1)	0.16	0.51
	Working memory (*WISC Index*)	5 (25.0)	4 (14.8)	0.77	0.31
	Processing speed (*WISC Index*)	5 (25.0)	5 (18.5)	0.32	0.42
Verbal learning (RAVLT)[b]	Learning (*PR*)	10 (55.6)	2 (7.7)	12.29^{***}	0.001^{**}
	Recall (*PR*)	9 (50.0)	3 (11.5)	7.93^{**}	0.007^{**}
	Recognition (*PR*)	4 (22.2)	1 (3.8)	3.57	0.08
Verbal learning (CMS)[b]	Immediate recall (*PR*)	3 (21.4)	1 (4.5)	2.47	0.15
	Delayed recall (*PR*)	6 (42.9)	2 (9.1)	5.64^{*}	0.03^{*}
	Delayed recognition (*PR*)	3 (23.1)	1 (4.7)	2.60	0.15
Sustained attention (CPT-II)[c]	Commission errors (*PR*)	1 (5.0)	1 (4.0)	0.03	0.70
	Omission errors (*PR*)	3 (15.0)	3 (11.1)	0.12	0.53
Divided attention (TAP)[b]	Commission errors (*PR*)	8 (44.4)	3 (11.1)	6.50^{**}	0.01^{*}
	Omission errors (*PR*)	4 (22.2)	4 (14.8)	0.41	0.40

Significance level: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. [a]Impaired when IQ score <85. [b]Impaired when percentile <16. [c]impaired when percentile >84.

reported an accuracy variable in a single test [e.g., 17] rather than examining different attentional variables derived from two different attentional measures. Secondly, the inattentiveness findings are based on data from BT patients gathered after undergoing predominantly multiple cancer treatments rather than at the time of initial diagnosis. Increased impulsivity might be a result of disturbed networks by expansion of the tumor or tumor-related transmitter imbalance that affect the limbic system which then leads to changes in arousal, possibly reflected in increased impulsivity measures.

Despite the attentional and mnemonic deficits of children with BT, there was no significant difference between the two patient groups in general intelligence this early in the course of treatment. Mean IQs of patients with BT lie within the normal range, thus confirming the results of Iuvone and colleagues.[17] Nevertheless, deficits in memory and attention as early as the time of diagnosis might make patients even more vulnerable to the damaging effects of the medical treatments to follow.[18,33] Since attention and learning processes are crucial for thriving in academic and social skills,[34,35] impairment in these functions at an early stage will put the patients at risk to fall behind same-aged peers. These deficits will further be aggravated by chemo- and radiation therapy. [33,36,37]

From a neuroanatomical point of view, these results are not unexpected: In contrast to other cognitive functions, memory and attention are based on the integrity of widely distributed neural networks and are therefore prone to be affected by nearly any tumor location and histology[38,39] as well as by intracranial high pressure due to tumor-related hydrocephalus prior to diagnosis. The impact of the localization of the damage seems to have only a limited impact on the neuropsychological outcome.[40] Disturbing connectivity in a developing system could have considerable impact on the development of cognitive abilities.[41] For example, memory problems have been documented in children treated for medulloblastoma,[42] or craniopharyngeoma[43] and in children with third[44] and fourth ventricle tumors[37] unlike patients treated for other tumors not involving the CNS or healthy siblings.[45]

Twenty percent of the children with BT in our sample showed impaired performance (<1SD) in at least four different cognitive tests compared to only 4% of the children in the sample without CNS involvement. Whereas in the first group impairment could mainly be explained by compromised connectivity in the brain, in the group without CNS involvement different cancer-induced mechanisms like immunologic processes may be responsible for a reduced cognitive performance.[46] Although there is a lack of research into long-term neurocognitive outcomes of children with BT, given their performance at diagnosis, it seems obvious that preexisting deficits in basal functions will likely impair further normal development of complex cognitive abilities.[47]

Emotion regulation is a process that demands a high amount of resources[48,49] and accordingly can adversely affect processing cognitive functioning if not successfully accomplished. In our two patient groups, the children themselves and their parents respectively rated their emotional distress, their social and behavioral difficulties and their quality of life quite similarly. It seems that children with BTs and children with other oncological diseases as well as their families were exposed to a comparable level of emotional and physical distress at diagnosis. Thus, the influence of anxiety, fear, and general distress on the performance in the neuropsychological assessment is likely comparable in both groups.

The generalizability of the present findings is limited in several aspects. The primary limitation of the report is the relatively small number of subjects. The small sample did not allow us to analyze in detail different specific variables potentially influencing memory and attention problems such as tumor histology, number and duration of neurological symptoms, presentation of hydrocephalus or epileptic seizures. Two studies with larger sample sizes[16,17] indicate that several medical factors might relate to cognitive problems in children with BT before surgery: histology and size of the tumor, age at onset, brain stem infiltration, presence of neurological deficits, longer symptom duration, hydrocephalus, and epileptic seizures.

Nevertheless, what stands out in this work is the comparison of cognitive performance in BT patients with that of children with non-CNS malignancies. Although our patient samples are heterogeneous, the results can be highly informative. In the event of a brain tumor, connectivity is interrupted and compromised. This is not the case in patients with oncological illnesses outside the CNS. This disturbance of connectivity could have considerable impact on further cognitive development.[41] The present findings emphasize the significance of and the high need for cognitive rehabilitation programs for children with BT [e.g., 36] to minimize or even prevent long-term cognitive impairment and to improve quality of life. Rehabilitation programs ought to start as early as possible during the treatment process, as soon as physical well-being and medical treatment allow. Thus, cognitive training programs targeting memory and attention should become part of the standard multi-disciplinary treatment of children with brain tumors.

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