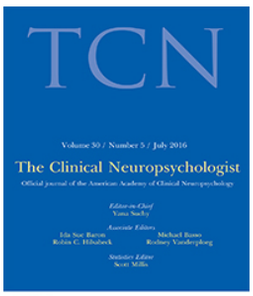

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Neuropsychological functioning in survivors of childhood medulloblastoma/CNS-PNET: The role of secondary medical complications

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ABSTRACT

Objective: To investigate the long-term cognitive consequences of malignant pediatric brain tumor and its treatment, and factors explaining variability in cognitive functioning among survivors. **Method:** A geographical cohort of survivors of pediatric medulloblastoma (MB) and supratentorial primitive neuroectodermal tumor (CNS-PNET), treated between 1974 and 2013, was invited to participate. Of the 63 surviving patients, 50 (79%) consented to participation. The participants were tested with a battery of neuropsychological tests covering a wide age range. Verbal cognition, nonverbal cognition, processing speed, attention, memory, executive functioning, and manual dexterity were assessed. The participants were between 5:5 and 51:11 years of age at time of assessment. Assessments took place on average 19 years after primary tumor resective surgery. **Results:** One participant had a severe intellectual disability. For the rest, IQ varied from 52 to 125, with a mean score of 88.0 (*SD* 19.7). Twenty-eight (56%) of the participants had full-scale IQ scores in the age-average range or above. Gender, age at operation, time since operation, the presence of secondary medical complications, and treatment variables explained 46% of the variability in IQ scores, $F(4,44) = 9.5$, $p < .001$. The presence of endocrine insufficiency in combination with either epilepsy and/or hydrocephalus was associated with lowered IQ, lowered processing speed, and memory impairments. **Conclusion:** Patients treated for childhood MB and CNS-PNET have a lifelong risk of medical sequelae, including impaired cognitive functioning. This study adds to the literature by demonstrating the importance of following neuropsychological functioning closely, especially processing speed, learning, and memory, in survivors who have multiple secondary medical complications.

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Introduction

Medulloblastoma (MB) and supratentorial primitive neuroectodermal tumor (CNS-PNET) are both embryonal malignant brain tumors: MB arises in the infratentorial compartment whereas CNS-PNET has a supratentorial localization. Together they comprise 10–20% of pediatric brain tumors (Johnson et al., 2014; King et al., 2017; Patel et al., 2014; Smoll & Drummond, 2012). MB is the most common form of malignant brain tumor in childhood (Bartlett et al., 2013; Moxon-Emre et al., 2014; Palmer, 2008; Patel et al., 2014; Ribi et al., 2005; Uday et al., 2015).

Treatment for MB and CNS-PNET is similar and is based on a multidisciplinary and risk-stratified approach, involving surgery followed by adjuvant radio- and/or chemotherapy (Laprie et al., 2015). Survival rates have steadily increased over the last decades, and five-year overall survival is 40–80%, depending on disease characteristics (Goschzik et al., 2018; Ramaswamy et al., 2016). In line with this, focus has shifted from survival only to also include quality of life post-treatment. This shift has brought with it an increased focus on the late effects survivors may experience (Na et al., 2018), as survival comes at a cost for children with MB and CNS-PNET. They experience cognitive impairments, academic and social challenges, hearing loss, epileptic seizures, endocrine insufficiency, secondary neoplasm, stroke, and problems with balance and coordination (Benesch et al., 2009; Chevignard et al., 2017; Doger de Spéville et al., 2018; Edelstein et al., 2011; King et al., 2017).

Cognitive impairments

There is considerable variation in cognitive functioning among MB/CNS-PNET survivors. Some are severely impaired, but the majority has IQ scores within the age-expected range (Câmara-Costa et al., 2015; Silber et al., 1992; Thorarinsdottir et al., 2007; Wegenschimmel et al., 2017; Yoo et al., 2016). However, many survivors score significantly below the age-average on tests of intelligence, with performance IQ on average being more reduced than verbal IQ (De Ruiter et al., 2013). In addition, specific challenges with inattention, slower processing speed, working memory deficits, and executive dysfunctioning are reported (Burgess et al., 2018; Chevignard et al., 2017; De Ruiter et al., 2013; Edelstein et al., 2011). The cognitive impairments are experienced as a challenge by the patients themselves; in a self-report study, 60% of 380 long-term survivors of MB/CNS-PNET reported learning or memory problems (King et al., 2017). The cognitive challenges persist; in one study, 11 of 14 patients with embryonal tumors (MB and CNS-PNET) had abnormal scores on neuropsychological tests two years after finishing treatment (Ehrstedt et al., 2016). Furthermore, the cognitive challenges can become more pronounced over time. A decrease in IQ scores, with a loss of 2–6 points per year starting a couple of years post-treatment, is reported across studies (Moxon-Emre et al., 2016; Mulhern et al., 2004; Palmer et al., 2001; Saury & Emanuelson, 2011). The reason for the decline is not loss of skills, but failure to learn and acquire new skills at the age appropriate rate, resulting in relatively lower functioning compared to what is expected of age (Mulhern et al., 2004; Palmer et al., 2001; Saury & Emanuelson, 2011). The lowered learning capacity has been attributed to impairments in processing speed, sustained attention, and working memory (Brière

et al., 2008; Doger de Spéville et al., 2018; Mabbott et al., 2008; Moxon-Emre et al., 2016; Reddick et al., 2003).

Different models have been proposed to explain the neurodevelopmental impact on cognition of brain tumor and its treatment. Palmer proposed a two-step model where slower processing speed was the critical core cognitive function affected, which then in turn led to reduced attention and working memory capacity. Over time, this negatively affected both intellectual outcome and academic achievement (Palmer, 2008). Another way of understanding the decline is to view executive functions, including processing speed, attention, and working memory, as equally affected (Wolfe et al., 2012). In an empirical test of the two neurodevelopmental models, a hybrid of the two models fitted the data best (King et al., 2019). Younger age at irradiation was associated with lower processing speed, and processing speed was the central cognitive skill most negatively affected. Processing speed did not have an independent effect on attention span, but negatively affected working memory, intelligence, and academic achievement (King et al., 2019). Taken together, this illustrates the negative cascading effects where core cognitive skills over time negatively affect IQ.

Factors contributing to cognitive impairments

Reasons for cognitive impairments include the neoplastic disease, antineoplastic treatment, the presence of secondary medical complications, and factors intrinsic to the child or the environment (Doger de Spéville et al., 2018; Raghubar et al., 2019). Characteristics of the child and the environment interact with the others. Treatment variables vary depending on the presentation of the disease and on the presence of secondary complications.

The neoplastic disease

In children with MB, damage to vermis and the dentate nucleus have been associated with worse outcome, including neurological and neuropsychological impairment, cerebellar mutism, and behavioral disturbances (Puget et al., 2009; Riva & Giorgi, 2000).

Treatment

In survivors of pediatric brain tumors, radiotherapy is associated with lowered IQ and inattentiveness (De Ruiter et al., 2013). The consequences depend upon total dose, fraction dose, and volume receiving irradiation (Doger de Spéville et al., 2018). Higher dose is associated with more negative outcomes (Mulhern et al., 1998; Ris et al., 2001; Silber et al., 1992), and in children with MB irradiation affecting the whole brain has more serious outcomes than irradiation of the posterior fossa region (Hoppe-Hirsch et al., 1995). Radiation therapy is associated with white matter lesions, and damage to the frontal lobes is common also with posterior fossa tumors (Ailion et al., 2017). Children treated with craniospinal irradiation often show white matter lesions shortly after treatment, and even though there might be subsequent growth of white matter, cognitive impairments remain (Partanen et al., 2018). There is an association between white matter volume and IQ scores (Reddick et al., 2003), and the decline in IQ scores

over time is only significant in MB patients with white matter lesions (Fouladi et al., 2004). The neural mechanism for this association is not well known (Bells et al., 2017; Glass et al., 2017), but an association between altered white matter microstructure, in the form of reduced neural synchronization, and functioning has been found in brain tumor patients (Bells et al., 2017). Furthermore, suboptimal integration and segregation of white matter networks correlate with executive functioning impairments (Na et al., 2018).

Other forms of treatment than radiotherapy are also associated with neural damage and cognitive impairments. A reduction in frontal white matter volume has been found in patients with MB who have undergone surgery, but not yet radiotherapy or chemotherapy (Glass et al., 2017). Chemotherapy, particularly methotrexate, is associated with white matter neurotoxicity in survivors of MB (Doger de Spéville et al., 2018; Riva et al., 2002). In a meta-analysis of 29 studies of survivors of pediatric brain tumors, chemotherapy explained 22% of the variance in IQ, while cranial radiotherapy explained 26% of the variability (De Ruiter et al., 2013).

Secondary medical complications

Increased intracranial pressure is often present at the time of MB/CNS-PNET diagnosis, and a significant proportion of patients (36%) requires postoperative shunting (Raimondi & Tomita, 1981). Epileptic seizures, also often a presenting symptom, persist in approximately 8–9% of survivors with MB, and a cumulative incidence of 34% in mixed group with MB/CNS-PNET patients has been reported (Ehrstedt et al., 2016; King et al., 2017; Suri et al., 1998; Ullrich et al., 2015). Endocrine dysfunction is also a known late effect after treatment for MB and CNS-PNET (Edelstein et al., 2011; Ribi et al., 2005).

However, despite the prevalence of the secondary medical complications, the consequences for cognitive functioning have not been extensively studied. It is known that increased intracranial pressure and epileptic seizures are associated with lowered cognition at time of diagnosis (Irestorm et al., 2018), that persistent hydrocephalus requiring shunting is negatively associated with processing speed and verbal comprehension (Moxon-Emre et al., 2014), and that pituitary dysfunction is associated with informant-reported executive impairments (Fox & King, 2016). The scarcity of research is somewhat surprising, as these medical complications are otherwise known to be associated with cognitive challenges. Cognitive impairments are reported in up to 50% of children with pediatric hydrocephalus (Vinchon et al., 2012), and epilepsy is associated with worse cognitive outcomes in children with other early-onset brain lesions, such as cerebral palsy (Stadskleiv et al., 2018). Childhood onset growth hormone deficiency (GHD) is associated with impaired hippocampal function, and treatment of GHD improves memory and attention (Arwert et al., 2006; Wass & Reddy, 2010). There might be several reasons why cognitive impairments in relation to secondary medical complications have not been extensively studied in survivors of pediatric brain tumors. It might be that the conditions are not considered damaging if they are well regulated, that is by shunt, anti-epileptic drugs or hormonal replacement therapy. It may also be that as the onset of complications can be many years post-

treatment (Ullrich et al., 2015), the effect is not captured due to missing long-term follow-up.

The child and the environment

Factors intrinsic to the child, such as age and gender, and environmental factors such as the family's socioeconomic status, adaptations available in school, and implementation of appropriate cognitive rehabilitation interventions might influence cognitive outcomes (Doger de Spéville et al., 2018). Younger age at time of diagnosis is associated with an increased risk of cognitive impairment (Edelstein et al., 2011; Mulhern et al., 2001), and older age at radiotherapy results in less decline in IQ scores (Mulhern et al., 1998; Silber et al., 1992). Younger age has particularly been associated with working memory impairments (King et al., 2019). Because of this, radiotherapy is avoided or delayed in very young children, although this strategy leads to a higher risk of recurrence and death. In a study of seven survivors of MB and CNS-PNET diagnosed before four years of age and initially treated with only surgery and chemotherapy, the IQ scores were at or above 90 for five of the children (Thorarinsdottir et al., 2007).

The literature on the effect of gender is somewhat ambiguous. Some studies report that gender is not related to cognitive outcome (Pulsifer et al., 2015; Shabason et al., 2019). Other studies report a difference. Reduced processing speed has been reported for both males (Irestorm et al., 2018) and females (Panwala et al., 2019). However, in the studies reporting an impact of gender, females seem to struggle more both on cognitive tasks and on measures of adaptive skills (Holland et al., 2018; Kautiainen et al., 2020; Panwala et al., 2019; Ris et al., 2001).

Survivors often report having few or no friends, and only 22% of adults have a partner (King et al., 2017; Ribi et al., 2005). Psychological and cognitive functioning is associated in survivors (Poggi et al., 2005). The traumatic experience of being diagnosed with and treated for a possibly life-threatening disease might influence not only the psychological functioning of the child and parents, including family dynamics, but also cognitive functioning (Marusak et al., 2018).

Research questions

Although the risk of cognitive impairments in survivors of pediatric MB/CNS-PNET is acknowledged, there are still gaps in our knowledge concerning the long-term consequences and in particular the relative importance of different risk factors. There is a scarcity of studies investigating neuropsychological impairments in relation to secondary medical complications, such as persistent hydrocephalus, epilepsy, and endocrine insufficiency. Furthermore, we are not aware of any study investigating all of these factors in combination and exploring the relative impact of factors intrinsic to the child, treatment related variables, and secondary medical complications upon cognition. The purpose of this study was therefore two-fold: 1) to describe cognitive functioning in a representative sample of long-term survivors of pediatric MB/CNS-PNET and 2) to investigate which of the factors – gender, age at diagnosis, time since diagnosis,

secondary medical complications, and treatment variables – contributed most to variability in different domains of cognitive functioning.

Methods

The study is part of a larger cross-sectional investigation of a geographical cohort of survivors of pediatric MB and CNS-PNET (Stensvold et al., 2020).

Participants

Participants were recruited from the entire geographical cohort treated for MB or CNS-PNET at Oslo University Hospital between January 1, 1974 and December 31, 2013. Of the 157 patients younger than 21 years of age at time of primary diagnosis, of whom 123 had MB and 34 CNS-PNET, 63 patients (40%) had survived. All, except one patient who had emigrated from Norway, were invited to participate, and 50 (79%) consented. As the aim was to investigate a complete geographical cohort, there were no exclusion criteria except that for practical purposes the participants had to be residing in Norway. The 13 nonparticipant survivors did not differ from the participants in terms of age at first surgery, gender, histology, and whether or not they had received radiotherapy.

Patient characteristics are summarized in Table 1. The participants, 25 males and 25 females, were between 5:5 and 51:11 years of age at time of assessment, with a mean age of 26;8 years. Forty-two (84%) of the participants had MB and eight CNS-PNET. All participants underwent surgery, and they were between two and 231 months of age at primary surgery. None had only performed biopsy, 43 underwent gross total resection, and five participants had performed more than one neurosurgery, which in two cases was due to tumor recurrence. Intrathecal methotrexate was part of the treatment for 15 of the 42 patients who received chemotherapy. Forty-four participants received irradiation. They received between 44.0 and 56.7 Gy of irradiation. All but one of the 44 received craniospinal irradiation. One participant received only local fractionated radiotherapy to parts of the left hemisphere without cerebrospinal irradiation. Radiotherapy was photon-based in all patients except the one who did not receive craniospinal irradiation; the latter patient had proton irradiation. Thirty-six of the participants received both chemotherapy and irradiation. Six patients, of whom five were younger than two years at time of surgery, did not receive radiotherapy, but they received both intravenous and intrathecal chemotherapy, which included methotrexate. Fifteen patients (30%), all who had received radiotherapy, experienced 23 secondary primary neoplasms.

The length of education for the 34 participants who were 18 years or older at time of assessment ranged from 10 to over 17 years, with a mean of 13 and a standard deviation (*SD*) of 1.8 years. Five had completed only the first 10 years, which comprise the compulsory education in Norway, 23 had completed secondary education, which in Norway is three years following compulsory education, and six tertiary education (college or university). As for employment, 13 worked part- or full-time, of whom nine were still studying and 21 received disability pensions.

Table 1. Treatment characteristics of all 50 participants.

Variable		N (%)
Therapy		
	One neurosurgery and chemotherapy	5 (10%)
	Two neurosurgeries and chemotherapy	1 (2%)
	One neurosurgery and craniospinal irradiation	8 (16%)
	One neurosurgery, focal irradiation, and chemotherapy	1 (2%)
	One neurosurgery, craniospinal irradiation, and chemotherapy	31 (62%)
	Two neurosurgeries, craniospinal irradiation, and chemotherapy	4 (8%)
Decade treated		
	1970–1979	
	Surgery and irradiation	2 (4%)
	1980–1989	
	Surgery and irradiation	4 (8%)
	Surgery, irradiation, and chemotherapy	9 (18%)
	1990–1999	
	Surgery and chemotherapy	2 (4%)
	Surgery and irradiation	1 (2%)
	Surgery, irradiation, and chemotherapy	9 (18%)
	2000–2013	
	Surgery and chemotherapy	4 (8%)
	Surgery and irradiation	1 (2%)
	Surgery, irradiation, and chemotherapy	18 (36%)
Treatment protocol		
	SIOP 1974	6 (12%)
	SIOP December 1983	7 (14%)
	UKCCSG/SIOP PNET 3	7 (14%)
	Baby Brain – UKCCSG Study CNS 9204	2 (4%)
	HIT – SKK`92	2 (4%)
	Swedish-Norwegian protocol for PNET after high-risk group	4 (8%)
	SIOP PNET 4	10 (20%)
	HIT SKK 2000, PNET $<$ 4 years	3 (6%)
	MET HIT 2000 BIS 4	3 (6%)
	MET HIT AB4 (M2–M4)	2 (4%)
	No protocol	4 (8%)
Late effects		
	Secondary primary neoplasm	15 (30%)
	Tumor recurrence	2 (4%)
	Postoperative persistent hydrocephalus	18 (36%)
	Epilepsy	16 (32%)
	Endocrine insufficiency	33 (66%)
	Panhypopituitarism	13 (26%)
	Hypothyroidism and growth hormone deficiency	8 (16%)
	Hypothyroidism	8 (16%)
	Growth hormone deficiency	4 (8%)
	Diplopia	8 (19%)
	Reduced hearing	20 (40%)
	Tinnitus	2 (4%)

Assessment of cognition took place on average 19 years after operation, varying between 3;3 and 40;5 years. Follow-up time was shorter for the younger participants, but for all it was more than three years from operation to time of assessment.

Secondary medical complications

Information about secondary medical complications was extracted from a record review of the participants' hospital records. Endocrine insufficiency was defined as a disturbance in hormonal regulation requiring hormone replacement therapy, with a

clinically significant lack of the production of either thyroxin, growth hormone, gonadal hormones, and or cortisone according to Common Terminology Criteria for Adverse Events, version 5.0 (National Cancer Institute, 2017). Participants on anti-epileptic medication were categorized as having epilepsy, and hydrocephalus was defined as having enduring postsurgical hydrocephalus that needed treatment, that is shunting (Fisher et al., 2014; Savarese, 2013).

Instruments

To quantify the neuro-oncological risk factors, the Neurological Predictor Scale (NPS) (Micklewright et al., 2008) was utilized. This is an ordinal scale for investigating the joint contributions of secondary medical complications and type of treatment (surgery, irradiation, and chemotherapy) received. Possible scores range from 0 to 11. It is divided into four sections. In the first section, where the presence of any secondary medical complication (endocrine insufficiency, epilepsy, and hydrocephalus) is rated, the possible maximum score is 4. In both the second, where the number of surgeries are rated, and the third, where type of radiation therapy is registered, the maximum score is 3. In the fourth section, the child can receive an additional point if having undergone chemotherapy. The scores from the four sections are then combined. The minimum score of 0 is given if the participant has not been diagnosed with any neurological conditions other than a brain tumor and did not undergo any treatment. A maximum score of 11 is given to participants who are a) prescribed seizure medications and diagnosed with hydrocephalus, who may also have a hormone deficiency in addition, b) have had more than one surgery related to the removal of the brain tumor, c) have received both whole-brain radiation and a "boost" to the site of the tumor, and d) have received chemotherapy. The NPS has previously been used in regression analyses to explore factors contributing to variability in cognitive functioning (Micklewright et al., 2008) and has been found to explain more of the variability in cognitive outcomes among survivors of pediatric brain tumors than any of the factors in isolation.

The Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler, 2007) or comparable tasks from other Wechsler tests (the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) (Wechsler, 2015) or Wechsler Intelligence Scale for Children (WISC) (Wechsler, 2017) were used to assess intelligence. The test battery further included Trail Making Test (TMT), Color-Word Interference (CWI) test, and Verbal Fluency (VF) test from Delis-Kaplan Executive Functions System (D-KEFS) (Delis et al., 2005), Digit span from either WISC or Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 2011), Connors' Continuous Performance Test (CPT), third edition (Conners, 2008), Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964; Strauss et al., 2006, pp. 786–804), Rey Complex Figure Test (RCFT) (Meyers & Meyers, 1995), and Grooved pegboard (Lafayette, 2002). The intelligence tests have Norwegian translations and adaptations, and the D-KEFS and RAVLT have Norwegian translations. All instruments used in this study are frequently used by neuropsychologists in Norway (Vaskinn & Egeland, 2012).

Scores within one *SD* of the age mean are interpreted as age-average. Scores more than two *SD* below the age mean were defined as low-range values. All results are

presented in the same direction; the results on CPT, where a high score originally implies a worse outcome, were transformed.

Procedure

The neuropsychological assessment was part of a two-day comprehensive medical examination and was scheduled in the morning of the second day. Assessments, which took between 1 ½ and 3 hours, typically with a 10- to 20-minute break midway, took place in a quiet room at the hospital. The tests were either administered by a licensed neuropsychologist (in 33 cases) or by graduate psychology students, supervised by the first author.

The standard test battery was administered to survivors of both MB and CNS-PNET. For 47 of the participants, a full-scale IQ was computed based on the four subtests from WASI-II. For one participant younger than six years of age at the time of assessment and one participant aged 11, who had just undergone an assessment of cognition for clinical reasons, tasks from WPPSI and WISC comparable to the ones included in the WASI (Vocabulary, Similarities, Block Design and Matrix Reasoning) were used. For these two participants, the mean scores from these tasks were used to compute verbal, performance and full-scale IQ.

For one participant, a cognitive quotient was estimated using test of verbal comprehension only, due to the severity of the cognitive and motor impairments. The participant was given a diagnosis of severe intellectual impairment. As the results were not based on a standardized form of administration, they are not included in the analyses.

Of the 47 participants administered the standard test battery, 36 (77%) were able to complete all tasks and four completed eight of the nine tests. The main reason for not completing the whole test battery was that some tasks were cognitively too demanding. Some tasks requiring writing/drawing (like TMT and RCFT) had to be left out if the participant had severe fine-motor impairments.

Statistics

The distribution of IQ scores did not violate assumptions of normality, with Shapiro–Wilk tests $p > .05$. Independent samples *t*-tests were computed to investigate whether type of tumor (MB versus CPN-PNET), age at time of assessment or millennium treated with radiation therapy influenced cognition, and to compare the test scores of participants without and with multiple secondary medical complications. Paired-samples *t*-tests were used to compare results from the same test. One-way analyses of variance, with Tukey tests to control for multiple comparisons, were used to compare differences between groups of participants.

To explore factors contributing to variability in cognitive functioning, a linear regression analysis was performed. The dependent variable was the IQ score; for 47 of the participants, this was computed based on the four subtests from WASI, and for two participants mean results from similar subtests from WPPSI and WISC were used. The independent variables were gender, age at operation, time since operation, and

the four sections of the NPS. The NPS does not include the known risk factors intrinsic to the child, such as gender, age at treatment, and time since treatment, and these were therefore added separately. Prior to interpreting the results of the regression analysis, its suitability was investigated. Collinearity statistics showed variance inflation factors below 2 (should be well below 10). A visual inspection of the Normal P–P plot and the scatterplot confirmed that the dependent variable was normally distributed, and there were no extreme outliers. Time from operation and NPS section 2 (number of surgeries) and section 3 (type of radiation therapy) did not correlate significantly with the dependent variable, but as there were no issues of multicollinearity, all variables were retained.

Ethics

All participants were given written information about the study, and informed consent was obtained from all participants. For participating children under 16 years of age and for adults with moderate or severe intellectual disability, caregivers gave consent on the participant's' behalf. The study protocol was approved by the Regional Committees for Medical and Health Research Ethics of the South-Eastern Norway Regional Health Authority (#2015/2362) and the Data Protection Officer at the Oslo University Hospital. The study was registered in ClinicalTrials.gov (NCT02851355). Ethical standards of the Declaration of Helsinki were followed.

Results

Mean IQ was 88.0 (*SD* 19.7) and varied from 52 to 125[1]. Table 2 presents an overview over the neuropsychological results for the 49 participants. Twenty-eight (56%) of the participants had IQ scores in the age-average range or above. Verbal IQ was significantly lower than performance IQ, $M(SD) = 86.6$ (18.6) vs 91.0 (19.0), $t(48) = -3.2$, $p = .003$.

Five (10%) of the 50 participants had IQ scores that were above the age-expected range, that is more than one *SD* above the age mean. Eleven (22%) of the participants had an IQ in the low range, that is more than two standard deviations below the age mean. For seven, both performance and verbal IQ scores were below 70, while four participants had skewed profiles with either verbal IQ ($N = 2$) or performance IQ ($N = 2$) above 70.

There were no significant differences in IQ between participants with MB and CNS-PNET, $M(SD) = 89.3$ (20.1) vs 81.1 (17.2), $t(47) = 1.08$, $p = .286$, between participants 18 years of age and younger and those older at time of assessment, $M(SD) = 89.1$ (21.0) vs 85.7 (17.3), $t(47)$, 0.57, $p = .573$, and between participants receiving radiation treatment before and after year 2000, $M(SD) = 84.9$ (18.7) vs 88.7 (20.9), $t(41) = -0.63$, $p = .532$.

From Table 2, it can be seen that participants used relatively longer time on the cognitively more complex tasks, such as sequencing and switching between different tasks, than on tasks measuring reaction time or fine-motor speed. On all measures of attention span, working memory, and cognitive flexibility, mean results were within

Table 2. Neuropsychological test results, with mean (*M*), standard deviation (*SD*), range (minimum to maximum scores), number (*N*) completing test and number/percentage (*N* (%)) of all 50 participants with age-average results (i.e. scores better than one *SD* below the age mean).

Domain	Test tasks	*M* (*SD*)	Min–Max	*N* done	***N*** **(%)** ***>-1SD***
IQ[1]	Four subtests from Wechsler[2] test	88.0 (19.7)	52–125	49	28 (56)
Verbal cognition					
	Wechsler Vocabulary	85.0 (19.8)	55–126	49	25 (50)
	Wechsler Similarities	87.9 (20.1)	55–121	49	33 (66)
Nonverbal cognition					
	Wechsler Block Design	90.9 (17.9)	58–121	49	28 (56)
	Wechsler Matrix Reasoning	90.7 (22.1)	55–124	49	33 (66)
Processing speed					
	CPT[3] hit reaction time	90.4 (18.4)	40–123	44	31 (62)
	TMT[4] visual scanning	73.6 (18.5)	55–115	44	14 (28)
	TMT number sequencing	77.1 (19.3)	55–115	43	16 (32)
	TMT letter sequencing	72.8 (21.5)	55–115	43	13 (26)
	TMT number/letter sequencing	76.3 (18.2)	55–115	42	16 (32)
	TMT motor speed	83.9 (19.3)	55–115	45	27 (54)
	CWI[5], color naming speed	75.3 (16.8)	55–115	46	18 (36)
	CWI, word reading speed	73.9 (18.5)	55–120	46	14 (28)
	CWI, inhibition speed	81.1 (19.7)	55–115	44	23 (46)
	CWI, switching speed	74.2 (19.3)	55–115	43	14 (28)
Attention					
	CWI, inhibition error	94.9 (17.7)	55–115	44	37 (74)
	CPT omission errors	91.1 (19.0)	40–109	44	34 (68)
	CPT commission errors	87.3 (15.8)	57–124	44	25 (50)
	Digit span	85.7 (15.3)	55–115	47	25 (50)
	RAVLT[6] list A trial 1	87.1 (12.3)	48 – 112	44	23 (46)
	RAVLT list B	85.0 (15.1)	57 – 118	47	23 (46)
Flexibility					
	CPT perseveration errors	88.6 (22.4)	40–108	43	32 (64)
	CWI, switching error	89.2 (18.5)	55–115	43	30 (60)
	VF[7], switching accuracy	88.8 (15.5)	55–125	44	31 (62)
Planning					
	VF, phonological fluency	90.1 (16.5)	60–125	43	26 (52)
	VF, semantic fluency	89.1 (17.2)	55–120	46	28 (56)
Memory					
	RAVLT learning phase	76.9 (20.5)	27–120	47	18 (36)
	RAVLT immediate recall	86.8 (20.5)	27–132	47	22 (44)
	RAVLT delayed recall	88.3 (18.9)	27–136	47	29 (58)
	RCFT[8] copy	76.0 (18.0)	55–111	45	15 (30)
	RCFT immediate recall	67.1 (28.3)	27–115	43	13 (26)
	RCFT delayed recall	65.5 (27.7)	27–115	43	13 (26)
	RCFT recognition	73.2 (26.0)	27–111	43	17 (34)
Manual dexterity					
	Grooved pegboard (dominant hand)	64.0 (28.3)	27–115	49	15 (30)
	Grooved pegboard (non-dom. hand)	52.0 (30.2)	27–114	48	11 (22)

Notes:
[1]IQ: Intelligence quotient based on the four subtests such as Vocabulary, Similarities, Block Design, and Matrix Reasoning;
[2]Wechsler tests used: Wechsler Abbreviated Scale of Intelligence ($N = 47$), Wechsler Preschool and Primary Scale of Intelligence ($N = 1$), and Wechsler Intelligence Scale for Children ($N = 1$);
[3]CPT: Conners' Continuous Performance Test, third edition;
[4]TMT: Trail Making Test, from D-KEFS;
[5]CWI: Color-Word Interference test, from D-KEFS;
[6]RAVTL: Rey Auditory Verbal Learning Test;
[7]VF: Verbal Fluency test, from D-KEFS;
[8]RCFT: Rey Complex Figure Test.

the age-expected range. There was no difference in memory span and auditory working memory, investigated by comparing digit span forward and backward, $t(45) = 1.1$, $p = .269$. On RAVLT, results from the learning phase were significantly lower than

Table 3. Linear regression analysis of variables contributing to IQ[1] variability.

	Standardized β	t	p
Constant		12.59	<.001
Gender	−0.28	−2.54	.015
Age at operation	0.28	2.49	.017
Time from operation	0.00	0.02	.988
NPS[2]	−0.52	−4.69	<.001

Note:
[1]IQ: Intelligence quotient based on the four subtests such as Vocabulary, Similarities, Block Design, and Matrix Reasoning from Wechsler Abbreviated Scale of Intelligence ($N = 47$), Wechsler Preschool and Primary Scale of Intelligence ($N = 1$), or Wechsler Intelligence Scale for Children ($N = 1$);
[2]NPS: Neurological Predictor Scale.

Table 4. IQ[1] scores, mean, and standard deviation (*SD*), for participants related to presence and type of secondary medical complications.

	N	*M*(*SD*)	**Significance testing[2]**
No secondary medical condition[a]	9	97.7 (10.8)	p=.008[a>e], p=.030[a>f]
Only endocrine insufficiency[b]	13	95.1 (18.3)	p=.009[b>e], p=.040[b>f]
Only hydrocephalus or only epilepsy[c]	7	104.3 (16.3)	p=.001[c>e], p<.006[c>f]
Endocrine insufficiency and hydrocephalus[d]	7	80.1 (17.0)	
Endocrine insufficiency and epilepsy[e]	8	69.6 (15.3)	
Endocrine insufficiency and/or hydrocephalus, and epilepsy[f]	5	69.8 (12.3)	

Note:
[1]IQ: Intelligence quotient based on the four subtests such as Vocabulary, Similarities, Block Design, and Matrix Reasoning from Wechsler Abbreviated Scale of Intelligence ($N = 47$), Wechsler Preschool and Primary Scale of Intelligence ($N = 1$), or Wechsler Intelligence Scale for Children ($N = 1$);
[2]One-way analyses of ANOVA with post hoc tests, Tukey correction to control for multiple comparisons between groups a-f.

results from first recall of list A, $t(43) = 4.9$, p<.001, recall of list B, $t(46) = 3.7$, $p = .001$, immediate recall of list A, $t(46) = -5.2$, p<.001, and delayed recall of list A, $t(46) = -5.4$, p<.001. Results from immediate and delayed recall on RAVLT were not significantly different, $t(46) = -0.7$, $p = .504$. The results on the copy part of RCFT were significantly better than on both recall conditions, $t(42) = 2.89$, $p = .006$ and $t(42) = 3.49$, $p = .001$ for immediate and delayed recall, respectively, but not better than the recognition part.

Manual dexterity was affected in the majority of participants, with only 30% having age-average performance with their dominant hand on a task requiring speedy coordination (Grooved pegboard). Sixteen of the affected participants were still able to trace a line with a pencil with an age-average speed (part five on the TMT).

Gender, age at operation, time since first surgery, and the variables included in the NPS – secondary medical complications and type of treatment (surgery, radiation, and chemotherapy) received –explained 46% of the variability in IQ scores, a significant contribution, $F(4,44) = 9.46$, p<.001. Age at operation, gender and NPS made unique contributions (see Table 3). Dividing the participants into three age-at-operation groups, a significant difference was found, $F(2, 46) = 6.78$, $p = .003$. Participants aged two to six years at time of treatment ($N = 17$) had significantly lower IQ, $M(SD) = 75.2$ (18.5), than participants younger than two years ($N = 6$), $M(SD) = 96.0$ (22.1), and older than six years ($N = 26$), $M(SD) = 94.5$ (16.1) at time of treatment. Five of the six

Table 5. Neuropsychological test results for participants with ($N = 19$) and without ($N = 30$) endocrine insufficiency in combination with either hydrocephalus and/or epilepsy.

Test tasks	*Endocrine insufficiency and hydrocephalus and/or epilepsy*		*t*	*p**
	NO M (SD)	***YES M (SD)***		
IQ[1]				
Four subtests from Wechsler[2] test ($N = 30, 19$)	96.8 (17.0)	74.1 (15.5)	4.7	<.001
Verbal cognition				
Wechsler Vocabulary ($N = 30,19$)	93.9 (17.2)	71.1 (15.2)	4.7	<.001
Wechsler Similarities ($N = 30, 19$)	96.4 (17.7)	74.6 (16.3)	4.3	<.001
Nonverbal cognition				
Wechsler Block Design ($N = 30, 19$)	98.2 (16.2)	79.5 (14.2)	4.1	<.001
Wechsler Matrix Reasoning ($N = 30, 19$)	98.8 (18.5)	77.8 (21.7)	3.6	.001
Processing speed				
CPT[3] hit reaction time ($N = 28, 16$)	92.0 (16.8)	87.6 (21.2)		NS
TMT[4] visual scanning ($N = 27, 17$)	79.4 (17.5)	64.4 (16.6)	2.8	.007
TMT number sequencing ($N = 28, 15$)	80.9 (18.9)	70.0 (18.7)		NS
TMT letter sequencing ($N = 28, 15$)	78.4 (20.8)	62.3 (19.4)	2.5	.018
TMT number/letter sequencing ($N = 28, 14$)	82.0 (17.1)	65.0 (15.2)	3.1	.003
TMT motor speed ($N = 27, 18$)	91.5 (16.2)	72.5 (18.3)	3.7	.001
CWI[5], color naming speed ($N = 28, 18$)	79.8 (15.4)	68.3 (17.1)	2.4	.022
CWI, word reading speed ($N = 28, 18$)	80.0 (18.7)	64.4 (13.9)	3.0	.004
CWI, inhibition speed ($N = 28, 16$)	86.8 (18.7)	71.3 (17.9)	2.7	.010
CWI, switching speed ($N = 27, 16$)	80.6 (63.4)	63.4 (16.2)	3.1	.004
Attention				
CWI, inhibition error ($N = 28, 16$)	97.9 (17.3)	89.7 (17.6)		NS
CPT omission errors ($N = 28, 16$)	93.6 (17.9)	86.7 (20.5)		NS
CPT commission errors ($N = 28, 16$)	88.9 (13.9)	84.3 (18.8)		NS
Digit span ($N = 29, 18$)	92.2 (13.1)	75.3 (12.5)	4.4	<.001
RAVLT[6] list A trial 1 ($N = 28, 16$)	89.3 (10.3)	83.3 (14.8)		NS
RAVLT list B ($N = 29, 18$)	88.8 (15.8)	78.9 (11.9)	2.3	.028
Flexibility				
CPT perseveration errors ($N = 27, 16$)	90.7 (20.8)	85.1 (25.1)		NS
CWI, switching error ($N = 27, 16$)	96.1 (13.7)	77.5 (20.1)	3.6	.001
VF[7], switching accuracy ($N = 27, 17$)	92.0 (15.6)	83.5 (14.3)		NS
Planning				
VF, phonological fluency ($N = 27, 16$)	93.7 (15.8)	84.1 (16.3)		NS
VF, semantic fluency ($N = 28, 18$)	96.8 (12.4)	77.2 (17.1)	4.5	<.001
Memory				
RAVLT learning phase ($N = 29, 18$)	83.7 (19.7)	65.8 (17.0)	3.2	.002
RAVLT immediate recall ($N = 29, 18$)	92.3 (20.2)	77.9 (18.1)	2.5	.017
RAVLT delayed recall ($N = 29, 18$)	93.7 (16.0)	79.5 (20.4)	2.7	.011
RCFT[8] copy ($N = 28, 17$)	84.5 (16.4)	62.2 (10.3)	5.0	<.001
RCFT immediate recall ($N = 28, 15$)	77.0 (24.7)	48.5 (25.6)	3.6	.001
RCFT delayed recall ($N = 28, 15$)	74.0 (26.5)	49.7 (23.3)	3.0	.005
RCFT recognition ($N = 27, 16$)	78.2 (23.1)	64.8 (29.2)		NS
Manual dexterity				
Grooved pegboard (dominant) ($N = 30, 19$)	73.3 (24.7)	49.3 (27.9)	3.1	.003
Grooved pegboard (nondominant) ($N = 30, 18$)	54.2 (32.2)	48.3 (27.2)		NS

Notes:
*Independent samples *t*-test, equal variances assumed;
[1]IQ: Intelligence quotient based on the four subtests such as Vocabulary, Similarities, Block Design, and Matrix Reasoning;
[2]Wechsler tests used: Wechsler Abbreviated Scale of Intelligence ($N = 47$), Wechsler Preschool and Primary Scale of Intelligence ($N = 1$), and Wechsler Intelligence Scale for Children ($N = 1$);
[3]CPT: Conners' Continuous Performance Test, third edition;
[4]TMT: Trail Making Test, from D-KEFS;
[5]CWI: Color-Word Interference test, from D-KEFS;
[6]RAVTL: Rey Auditory Verbal Learning Test;
[7]VF: Verbal Fluency test, from D-KEFS; and
[8]RCFT: Rey Complex Figure Test.

participants younger than two years had not received radiotherapy, while 16 of the 17 participants aged two to six years had. Male participants had significantly higher IQ scores than females, $M(SD) = 95.2\ (18.2)$ vs $81.1\ (19.0)$, $F(1,47) = 6.98$, $p = .011$. The variables included in the NPS alone explained 33% of the variability in IQ scores. Analyzing the relative importance of the variables included in NPS, it was found that whether or not the participant had received radiotherapy, $t = -2.50$, $p = .017$, and the presence of secondary medical complications, $t = -2.99$, $p = .005$, both made unique independent contributions. Dose of radiotherapy received did not correlate significantly with IQ, $r(48) = .13$, $p = .402$. The presence of secondary medical complications explained 11% of the variability. One-way ANOVA showed significant differences between the participants depending on number of secondary medical complications, $F(5,43) = 6.64$, $p < .001$. Post hoc tests showed that participants without or with only one medical complication scored significantly better than those who had endocrine insufficiency in combination with either epilepsy or hydrocephalus, or both (see Table 4). The participants with multiple secondary complications had particular challenges with processing speed, learning and memory, and also scored significantly lower on all the subtests from the intelligence tests (see Table 5).

Discussion

Mean IQ scores and the majority of the mean results on the neuropsychological tests were below the age-average, but within one standard deviation of the age mean. There was considerable variability in cognitive functioning among the survivors; 10% functioned well above what was expected for age and 14% had an intellectual disability.

Not all of our participants were able to complete all tests as some tasks were too demanding cognitively or motor-wise. In order not to underestimate the frequencies of impairment in the different cognitive domains among survivors of malignant pediatric brain tumors, we have presented the proportion of participants scoring as expected for age or better (i.e. better than one standard deviation below the age mean), implying that the remaining participants have challenges in this area. The results show that the proportion of participants with age-expected results varied in the different areas: from 66–74% obtaining age-expected results on tests of abstraction and logic reasoning (Similarities and Matrix Reasoning from WASI) and ability to avoid errors due to inattention or impulsivity (omission and commission errors on CPT) to 22–32% obtaining age-expected results on test of manual dexterity, processing speed and recall of visual memory.

We found that processing speed was reduced across a number of different tests among the survivors, and in particular among those with endocrine insufficiency and epilepsy and/or hydrocephalus. These findings lend support to neurodevelopmental models where core cognitive deficits, and in particular processing speed, have been proposed to have negative cascading effects (King et al., 2019; Mulhern et al., 2004; Palmer, 2008; Wolfe et al., 2012). However, these models have not included the effect upon memory, which in our study also seems to be substantial. The role of verbal and

visual memory, and how this is related to processing speed, executive functioning, and IQ, needs to be further investigated.

There were several factors contributing to the variability in cognitive functioning, and the presence of late effects, as examined by using the NPS, was one of them. Patients with endocrine insufficiency in combination with either epilepsy and/or hydrocephalus had lower functioning in several cognitive domains compared to participants without this late effect. The difference was substantial, in many areas exceeding one *SD* in mean standardized scores. It was particularly notable with regard to recall of visual and verbal information; however, also processing speed, nonverbal cognition, and verbal cognition were affected.

The association between endocrine insufficiency and cognition in survivors of malignant brain tumors has to our knowledge not been previously investigated by assessing the cognitive skills of the survivors, only by proxy-reported performance of executive functioning (Fox & King, 2016). Furthermore, we have found no study reporting on the association between learning and memory impairments and secondary medical complications. The most common endocrine sequelae were GHD, hypothyroidism, and adrenocorticotrophic hormone deficiency. There is a strong correlation between development of pituitary hormone deficiencies, which often arise years post-treatment, and total radiation dose received (Uday et al., 2015). The pituitary gland lies in the immediate vicinity of structures important for memory, such as the hippocampus and corpus mammillare (Brodal, 2013), and this region may be directly affected by irradiation. In our study, all participants with endocrine insufficiency had received radiotherapy, but not all that had received radiotherapy developed endocrine insufficiency.

Time since diagnosis and whether or not the patient had received surgery and chemotherapy contributed to the variability in cognitive functioning, but did not uniquely influence test results. Whether the patient had received radiotherapy did, but radiation dose received was not related to IQ. This reflects that the vast majority of our participants received similar doses. Age at operation did make an independent contribution. It seems likely that an interaction effect is the explanation for the importance of age; the youngest and the oldest participants had higher IQ scores than children between two and six years at time of treatment, and five of six participants in the youngest age group had not received radiotherapy (Stensvold et al., 2020).

Male participants scored better on tests of intelligence and had a faster hit reaction time, $M(SD) = 97.1$ (12.8) vs 83.6 (20.8), $F(1, 42) = 6.74$, $p = .013$ on the CPT, but not on other tasks measuring processing speed. There has previously been some conflicting results regarding gender and processing speed. In one previous study (Irestorm et al., 2018), where processing speed was measured by tasks from Wechsler tests, male gender was associated with worse outcome. In another study (Panwala et al., 2019), where processing speed was measured by an oral task, females had lower processing speed than males. Our findings, namely that males did better only on a reaction time test and did not have faster processing speed on more cognitively demanding tasks, suggest that the role of gender in relation to processing speed should be further examined.

Some of our findings may seem contradictory to previous results. Opposed to others (Brière et al., 2008; De Ruiter et al., 2013), we found performance IQ to be better preserved than verbal IQ. One reason might be that in WASI, where there are less timed measures included in the performance score than in the other Wechsler tests, the

results are not confounded with lowered processing speed (Wegenschimmel et al., 2017). In another study where WASI was employed, verbal IQ was also lower than performance IQ (Edelstein et al., 2011), lending support to the role of processing speed (Burgess et al., 2018). It therefore seems that verbal cognition and processing speed, and not necessarily visual-spatial cognition, are more affected in the survivor group. Furthermore, we found no evidence that focused attention (auditory memory span), inattentiveness, or impulsivity was particularly challenging when investigating the results from the whole group. On the contrary, the mean results on tests of accuracy (such as number of errors made in the switching conditions on Color-Word Interference and on verbal fluency tests, as well as number of omission and commission errors on the CPT) were all within the age-average range. Neither did attention span capacity seem to be particularly vulnerable to distracting stimuli, as recall of list B was equal to first recall of list A, and both mean scores were within the age-average span, on the test of verbal learning and memory. This contrasts with findings reported in a meta-analysis where challenges with inattention were reported (De Ruiter et al., 2013). However, also in the meta-analysis, hit reaction time and number of commission errors did not differ significantly from the normative sample. One reason for the difference in omission errors found in our study, where the mean score was in the age-average range, and the meta-analysis, where the group of survivors made significantly more errors of omission than the normative sample, might be that the latter sample was more heterogeneous and included more patients with a supratentorial tumor location. In line with previous research, however, we found a reduction in processing speed. Based on this, it seems that in our sample, the accuracy displayed was obtained at the expense of speed.

The memory impairments found in our sample were evident both for learning of verbal and visual material. Analyzing the results on the verbal tasks, the participant's attention span and long-term retrieval were significantly better than their learning score. This indicates that the core challenge is a reduction in capacity; the participants are able to focus their attention upon a more limited number of elements and memorize this information, but cannot cope with learning the same amount of new information as expected for their age. The same is evident on the test of visual memory, where the participants recalled significantly fewer visual details than they were able to identify when given a visual recognition test. It might be that the core challenge explaining these findings is a difficulty with independently organizing the material that has to be learned: to group words on the RAVLT into larger subunits and to organize the whole versus parts from the complex visual figure on RCFT. This interpretation would be in line with findings from a study where RCFT was used as a measure of executive functioning, and they found reduced planning skills in a group of survivors of pediatric brain tumors, compared to a demographically matched control group (King et al., 2015).

Clinical implications

Our findings supplement the growing body of evidence showing that as a group, survivors of malignant pediatric brain tumors are at risk of clinically significant cognitive impairments. Our findings complement previous studies by highlighting the role of memory impairments. Furthermore, it adds to the literature demonstrating that even

years after completing treatment, cognitive sequelae can be found. The results strongly suggest the need for a systematic long-term multidisciplinary follow-up, including comprehensive and repeated cognitive assessments, also after pediatric brain tumor survivors have reached adulthood, as late effects might not be noticeable in the first years post-treatment (Doger de Spéville et al., 2018).

Studies from other countries have highlighted that outcome after treatment for pediatric malignant brain tumors also depends upon environmental factors, such as parental education and the family's social–economical background (Ach et al., 2013; Kieffer et al., 2019). Norway is a quite homogenous society with a welfare state, where medical follow-up and education, including at College and University level, are free. This adds to the seriousness of our results, as the educational and vocational outcome of our participants cannot be explained by the social–economical background of the families, only by the illness and its treatment.

Identifying cognitive impairments is just the first step and should be followed by appropriate interventions. Cognitive impairments not only impact academic success, but also affect other aspects of life such as work opportunities, social functioning, societal participation, intimate relations, and quality of life (King et al., 2017; Ribi et al., 2005). Interventions should therefore include psychological support to cope with the unwanted late effects and social isolation many survivors experience, as well as targeting cognitive functioning directly. Group interventions focused on improving executive skills, attention, and memory are recommended for children (Laatsch et al., 2007; Slomine & Locascio, 2009), and it is recommended to actively include their parents in the interventions (van't Hooft & Norberg, 2010). Assistive technology, such as memory planners for patients with memory impairments, may be beneficial. If a patient temporarily or for a longer period of time loses the ability to speak due to posterior fossa syndrome/cerebellar mutism (Levisohn et al., 2000), alternative means of communication, such as boards or tablets with symbols, should be implemented immediately to alleviate some of the severe stress experienced when losing the ability to express oneself (Costello, 2000; Fried-Oken et al., 1991).

Some visual tasks seemed more challenging than verbal; the participants scored lower on tasks of visual recall than on a task of verbal recall and took relatively longer time scanning complex visual material and crossing out target symbols than what could be explained by reduced fine-motor skills. On the other hand, they scored lower on tasks included in the verbal IQ than on tasks included in performance IQ. This finding highlights that solving the performance tasks depends upon more than just visual-perceptual skills as participants might recruit a combination of visual and verbal logical reasoning skills to solve the performance tasks. Alternatively, this finding emphasizes the need for a multidisciplinary team approach to assessing visual functioning, visual perception, and cognition.

The present study highlights an increased risk of cognitive impairments in survivors of malignant pediatric brain tumors, but this does not imply that all survivors experience them or that all impairments are severe. Even though mean IQ score was below the age-average, the majority of participants in our study had IQ scores in the normal range. This is in line with other studies, where the majority of studies reporting reduced IQ still report on mean scores within two standard deviations of the age mean (De Ruiter et al., 2013; Edelstein et al., 2011). When presenting findings to

parents, other family members, and the patients, it is important to stress that no conclusions can be drawn on the individual level without a thorough neuropsychological assessment. Furthermore, even in areas where most survivors struggle, such as recall of visual information, as many as 30% still obtain scores within the age-average range. Parents need nuanced information where the risk of cognitive impairments is not neglected, and the need for continued assessments and interventions is presented, without painting a too bleak picture of the future.

Strengths and limitations

This paper reports on the neuropsychological outcomes of a representative, geographical sample of survivors of malignant pediatric brain tumors where 80% of the eligible participants consented to participation. The neuropsychological findings are not based on older case notes, but on a current assessment of the participants with the same test battery where 80% of the sample completed all or all but one of the tests. Furthermore, all participants were assessed, and none were deemed nonassessable due to the severity of their motor impairments, although some tests, which involved drawing, had to be skipped. To increase replicability of our findings, we did not include the IQ score from the participant with severe intellectual impairment who was not assessed in a standardized manner. However, to represent the vast variability in functioning and in order not to underestimate the frequency of impairments, the participant is included when calculating the percentage of participants with results in the normal range. The cognitive assessments were undertaken in parallel with a comprehensive medical examination, making it possible to investigate the relationship between cognition and late medical effects. Furthermore, it is the strength that secondary medical complications were classified using the NPS, which makes comparison with other studies of late effects more transparent.

The study also has limitations. First, the test battery did not include a test of visual memory that did not demand manual dexterity. The results on tests of manual dexterity (Grooved pegboard) are the area where the participants scored the lowest – reflecting that even though they were able to write and draw, they struggled with more advanced fine-motor activities. This might have influenced the results on the visual memory test RCFT. However, as the results on the visual recognition part – where the participants only needed to point – also were below the age-average range, this cannot fully explain the findings. Furthermore, finding that participants scored significantly better on the copy part of RCFT than on the recall parts supports this inference. Secondly, it is a limitation that not all participants were assessed with all tasks, yielding some missing data. For example, CPT was completed by 44 of the 50 (88%) participants. The reasons for the missing data were mixed: two participants were too young, and for three the task was cognitively too demanding, whereas one became too tired to complete the test. Finally, it is also a limitation that the sample – although representative – was not larger. This, of course, reflects the size of the population that the sample was drawn from, but also that the survival rate was only 40%. Thus, the survival rate was in the lower end of the continuum reported in international studies. One reason for this is that patients treated more than 40 years ago, when survival rates were lower, were also included. However, regional differences in survival rates in Norway have been found

(Solheim et al., 2011; Stensvold et al., 2019). The low survival rate might also have influenced test results in unknown ways. It is therefore recommended to replicate the investigations of this study in a national cohort, in order to control for this variability.

Conclusion

This study has investigated the relative importance of variables intrinsic to the child, treatment-related variables, and the role of secondary medical complications on cognitive abilities in MB and CNS/PNET survivors. By examining these factors in combination, the study adds to the literature.

Although the majority of survivors of malignant pediatric brain tumors have an IQ within the age-expected range, cognitive functioning varies considerably in the group. One factor explaining this variability, in this group where the majority had received large doses of radiotherapy, was the presence of medical late effects – particularly endocrine insufficiency in combination with either epilepsy and/or hydrocephalus. Due to the increased risk of cognitive impairments, long-term multidisciplinary follow-up, including neuropsychological assessments, is recommended. The follow-up should continue into and beyond young adulthood as functional impairments are not always noticeable at a younger age or closer to treatment. From a cognitive point of view, it is in particular recommended to investigate memory and processing speed in survivors who have endocrine insufficiency in combination with other medical complications, to enable the implementation of appropriate interventions as early as possible.

Note

1. Mean IQ was 86.7 (*SD* 21.5) if including the participant with a severe intellectual disability.

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List of abbreviations

Acronym	Full text
CNS-PNET	Supratentorial primitive neuroectodermal tumor
CPT	Connors' Continuous Performance Test
CWI	Color-Word Interference Test (from D-KEFS)
D-KEFS	Delis-Kaplan Executive Functions System
GHD	Growth hormone deficiency
IQ	Intelligence quotient
MB	Medulloblastoma
NPS	Neurological Predictor Scale
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
TMT	Trail Making Test (from D-KEFS)
VF	Verbal Fluency test (from D-KEFS)
WASI	Wechsler Abbreviated Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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