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RESEARCH PAPER

Cognitive performance of medulloblastoma tumour survivors related to the area of cerebellum damage

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ABSTRACT

Background: The aim of the study was to determine the relationship between a damaged cerebellum area and the cognitive performance of medulloblastoma tumour survivors. Also, age-based differences in cognitive performance were tested.

Materials and methods: Magnetic resonance imaging (MRI) technique was used to obtain brain images of survivors. The cognitive performance was tested using Wechsler Intelligence Scale for Children Revised (WISC-R) and Wechsler Adult Intelligence Scale (WAIS). Statistical analysis was performed with highly robust permutation tests.

Results: There were two anatomical features strongly influencing the cognitive performance of survivors. The extension of the foramen of Luschka had a negative impact on the overall verbal IQ score and some non-verbal scales while the excision of the middle part of the vermis influenced scores in such scales as arithmetic and picture completing.

Conclusions: Children with postoperative damages in the area of the middle part of the vermis are more likely to suffer from cognitive dysfunctions after the end of the treatment.

Keywords: medulloblastoma; cognitive performance; cerebellum; MRI

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Introduction

In connection with the increasing number of cancer patients and greater survivor ratio, increasingly, researchers are interested in long-term sequelae of both cancer and cancer treatment. Usage of multidimensional and specialized treatment, including surgery and recent chemotherapy and radiotherapy protocols, lead to the growth in the number of child cancer survivors who are vulnerable to negative late effects of applied therapies. The effects concern up to 62% of child patients treated for cancers. The children with the most complications are those treated for central nervous system (CNS) tumours [1]. Brain tumours are the second most common form of childhood cancer, following leukaemia, comprising 20% of new diagnoses [2,3].

Childhood brain tumour (BT) survivors are at increased risk for cognitive impairments because of disease and treatment-related factors [2, 4–6]. Research suggests that attention [7,8], working memory disorders [9] and lower general IQ might occur as the most crucial long-term cognitive symptoms [4, 10–12].

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Ris et al. [13] in their longitudinal study, indicated that a decline in IQ level reached up to 17.4 points on the Wechsler scale four years after radiotherapy. Hoppe-Hirsch et al. [14] provide similar data from five years follow-up because 42% of patients were found to have an IQ lower than 80. Craniospinal irradiation (CSI) doses, younger age at the time of treatment, and time since treatment seem to be the crucial factors for patients' mental development [4, 13]. Much research shows that IQ scores are related to the failure to make age-appropriate gains over time, as opposed to actual loss of skills [15, 16].

Localization and size of the tumour are also vital factors for cognitive performance [16, 17]. Children with infratentorial tumours, like medulloblastoma, usually have a greater cognitive load than those with supratentorial tumours [16]. This is related to the frequent occurrence (70–80% cases) of obstructive hydrocephalus, which constricts the flow of cerebrospinal fluid.

The most frequent negative aftermath of neurochirurgical procedures is posterior fossa syndrome [18] also known as cerebellar mutism, which occurs in up to 31% of children with infratentorial tumours. These disorders present 24–48 hours after surgery but usually improve over time when appropriate rehabilitation is used [16]. Some research indicates an overall lower level of performance in cognitive tasks when this syndrome occurs [19].

The aim of the present study was to identify the anatomical structures where damage could be linked to the cognitive function of children with medulloblastoma. The hypothesis was that damage to the medial structures (vermis cerebelli) was a strong predictor of cognitive outcome.

Material and methods

Participants

13 participants between 4 and 17 years old at the time of diagnosis were included in this study. Eligibility criteria required for participants to have completed oncological treatment, at the time of examination, be in complete remission, preferably 3 years or more after the end of the therapy. Three subjects did not meet the 3-year-post-treatment criterion, and were included based on the remaining conditions. The study was approved by the Institutional Review Board. Written informed consent was required prior to participation.. The mean age at the time of examination was 16.64 (range 7.00–26.00). The mean time of diagnosis was 9.67 years (range 4.00–17.00 years). The mean follow-up time after the completion of treatment was 6.64 years (range 1.00–10.00 years) in Table 1.

Table 1. Demographic characteristic of participants

ID	Sex	Age at diagnosis	Age at the end of treatment	Range of treatment years	Range of follow-up time	Age at examination	Risk group
Subject1	Female	9.5	10.5	1	4.5	15	SR
Subject2	Female	16	18	2	2	20	HR
Subject3	Female	4,5	7	2.5	6	13	HR
Subject4	Male	17	19	2	6	25	SR
Subject5	Male	9.5	11	1.5	10	21	SR
Subject6	Male	8	9.5	1.5	5.5	15	SR
Subject7	Female	4	5.5	1,5	2.5	8	HR
Subject8	Female	7.5	10	2.5	1	10	HR
Subject9	Male	12.5	14	1.5	7	21	HR
Subject10	Female	17	18.5	1.5	5.5	24	HR
Subject11	Male	6	7	1	10	17	HR
Subject12	Male	16.5	17.5	1	7.5	25	SR
Subject13	Male	4	5	1	2	7	HR

SR — standard risk; HR — high risk

Procedure of treatment

Treatment of all children was conducted according to the Standardized Brain Tumours Treatment Protocol applied in Poland. Initially, patients undergo a surgical procedure to mechanically reduce the mass of the tumour and to obtain material for histopathological assessment. Only patients with diagnosed medulloblastoma tumours were included in further study. Children were classified into two risk groups: standard risk (SR) and high risk (HR). These groups were based on stratifying factors such as histopathological type of medulloblastoma, size of excised tumour tissue during surgical procedure documented by MRI, presence of metastases in the brain or spinal cord, and presence of cancer cells in cerebrospinal fluid. Anaplastic type of tumour, leaving more than 1 cm^3 of cancer tissue in the first procedure and presence of metastases, qualified the patient to the HR group. This group assignment was related to more aggressive chemotherapy, higher doses of radiotherapy, and longer postsurgical treatment.

Radio- and chemotherapy

Chemoradiotherapy (CRT), including intensity-modulated radiation therapy, was delivered over 6 weeks with a prescribed dose of 24 Gy/13 fractions on CNS and boost to whole posterior fossa (or tumour bed): 54 Gy/30 fractions in SR group and 36 Gy on CNS, 54 Gy/13 fractions and boost to whole posterior fossa (or tumour bed in HR group). All children after surgery received 4 cycles of chemotherapy, depending on their weight. After radiotherapy 5 (SR group) to 8 (HR group) chemotherapy cycles were applied as well.

MRI measures

All children had an MRI examination at the end of treatment. The protocol contained T2 FLAIR, diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI) and 3D BRAVO sequences in the transversal plane and 3D CUBE FLAIR sequence in the sagittal plane.

The morphological data analysis included the following:

- evaluation of tumour bed volume and extension of the IV ventricle of the brain;
- division of the cerebellum into three areas containing such main anatomical structures as the vermis, intermediate zone of the cerebellum, and lateral zone of the cerebellum; the aim was to assess the range of postprocedural and post-therapeutic changes;
- volume symmetry evaluation of cerebellum hemispheres and cerebellum limbs;
- evaluation of the foramen of Luschka extension;
- evaluation of water flow disorders in DWI sequence correlated with late phase (at least 3 years after treatment) apparent diffusion coefficient (ADC) map;
- evaluation of fibres distribution and symmetry in DTI;
- detailed evaluation of excised structural fragments;
- evaluation of accompanying signal disorders, especially gliosis.

Cognitive assessment

The intelligence tests used were the Wechsler Intelligence Scale for Children Revised (WISC-R) and the Wechsler Adult Intelligence Scale (WAIS). Both instruments are well-validated, belong to the same group of tools, and assess widely used measures of cognitive ability. Composites and IQ scores were converted to a common standard score (M = 100; SD = 15).

Statistical analysis

The analysis was conducted with the R language and RStudio [20]. To import the data, the readxl package was used. To manage the data, we used dplyr, tidyr, magrittr, and openxlsx packages. For computing, we used the coin package with permutation tests, rstatix, and psych.

The study's database consisted of two parts. The first contained anatomical data from magnetic resonance imaging (MRI) and the second contained cognitive data. In addition, socio-demographic data such as sex and age were entered.

Descriptive statistics were calculated for the continuous variables: cognitive data, tumour bed volume (TBV), the age at diagnosis, and cognitive performance indicators (Supplementary File — Tab. S1). Furthermore, Shapiro-Wilk's tests of normality were performed. For the rest of the MRI data, which includes only nominal variables, sample size and percentages were computed (Supplementary File — Tab. S1).

To test the experimental hypothesis concerning the relationship between anatomical features and the cognitive performance of survivors, statistical analysis was performed. Owing to the small sample sizes, highly robust permutation tests of independence [22] were used to determine differences between groups (Supplementary File — Tab. S2). The conditional null distribution was approximated by Monte Carlo resampling [23]. To determine the effect size, Cohen's *d* coefficient was calculated [24].

Results

Two strong discriminative factors were discovered. The first was the extension of the foramen of Luschka Table 1, and the second was the excision of the middle part of the vermis depicted in Figure 1, Table 2.

The extension of the foramen of Luschka and the excision of the middle part of the vermis were both correlated with the lower cognitive performance of survivors (Tab. 2 and 3), But also associated was the younger age at diagnosis of medulloblastoma (Tab. 4).

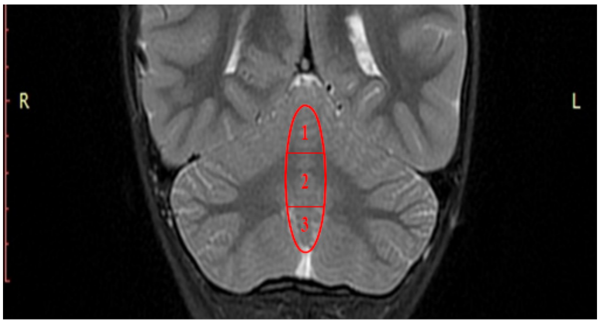

Figure 1. Division of the vermis: 1 — upper part, 2 — middle part, 3 — lower part

According to the standards of interpretation provided by Cohen [24], Cohen's *d* coefficient suggests big effect sizes in all presented cases.

Analysing the results presented in Table 4 we can see no statistically significant difference in cognitive performance between children with an age at diagnosis higher than 8.5 and the standard norm. In children with an age at diagnosis less than 8.5 years significant or nearly significant differences were seen in two verbal subscales and one nonverbal subscale, as follows:

- arithmetic, a verbal task that measures immediate memory and focus; requires the ability to perform mathematical calculations. The examiner reads a mathematical problem and the individual is required to complete the calculation without the use of paper and pencil. Arithmetic measures attention and memory, but also requires quick recall of math facts and functions and general proficiency in basic math calculations. No visual information or motor response is required;
- vocabulary, a test that measures word knowledge and the ability to verbally express the definition of words. Words are presented both visually (in large print) and orally to the student. This task requires minimal receptive and expressive vocabulary and no motor response is required. An appropriate definition can be a single word (synonym). The questions tend to tap information and experience learned through daily life and in the classroom. Disorders in this field can indicate impaired knowledge acquisition;
- coding, visual, paper and pencil tasks requiring individuals to match numbers with symbols

Table 2. Significant permutation independence tests for Wechsler Intelligence Scale for Children (WISC), similarities and picture ordering

Variable	Foramen of Luschka extended				Z	p	Cohen's d
	No		Yes				
	M	SD	M	SD			
IQ verbal	101.71	18.78	78.80	13.46	1.96	0.048	-1.49
IQ performance	103.29	14.75	82.20	25.99	1.64	0.100	–1.15
IQ full	105.33	12.40	76.00	20.58	2.13	0.028	–2.05
Similarities	12.00	2.58	7.00	3.67	2.19	0.020	–1.79
Pictures ordering	11.43	3.10	7.00	3.39	1.98	0.048	–1.51
Age of diagnosis	11.79	5.33	6.70	2.66	1.74	0.091	1.21
End of treatment	13.43	5.22	8.10	2.56	1.83	0.066	1.30

M — mean; SD — standard deviation; Z — measures the distance between a data point and M using SD; Cohen d — effect size measurement

Table 3. Significant permutation independence tests for arithmetic, picture completing, age of diagnosis and age at the end of treatment

Variable	The middle part of the vermis excised				Z	p	Cohen's d
	No		Yes				
	M	SD	M	SD			
IQ verbal	110.00	4.00	86.22	19.58	1.79	0.078	1.68
IQ performance	114.00	6.00	88.00	21.54	1.78	0.065	1.64
IQ full	112.00	5.57	85.71	20.78	1.78	0.066	1.73
Arithmetics	12.00	1.00	5.89	4.11	2.05	0.034	−1.81
Pictures completing	14.33	1.53	8.44	3.47	2.19	0.023	−2.03
Age of diagnosis	15.50	2.60	7.72	3.95	2.34	0.010	−2.29
End of treatment	17.17	2.75	9.22	3.80	2.39	0.010	−2.41

M — mean; SD — standard deviation; Z — measures the distance between a data point and M using SD Cohen d — effect size measurement

Table 4. The results of one sample t-student tests for two age groups based on the control values provided by Ryan et al. [25]

Variable	Tested value	≤ 8.5 years old			> 8.5 years old		
		M	SD	p	M	SD	p
Similarities	10.20	9.33	2.66	0.461	10.50	5.05	0.890
Vocabulary	10.48	6.67	3.72	0.054	9.67	3.27	0.569
Information	10.25	7.17	3.31	0.071	9.00	4.38	0.516
Block design	10.30	8.50	4.23	0.345	8.33	4.50	0.333
Visual puzzles	10.52	11.50	2.67	0.409	9.83	2.64	0.552
Digit span	10.60	9.50	3.73	0.502	10.83	2.93	0.853
Arithmetic	10.43	5.00	2.68	0.004	9.83	4.79	0.773
Coding	10.78	5.83	3.31	0.015	9.17	5.23	0.484

M — mean; SD — standard deviation

based on a key at the top of the page by drawing the correct symbol in the boxes provided. Coding measures visual processing speed, short-term visual memory, and the ability to shift eye gaze efficiently back and forth between the key and the responses. This task requires fine motor skills (using a pencil) but does not require expressive language. Minimal demands are placed on receptive language. It also assesses the ability to sustain focus for two minutes.

Discussion

Children who have been treated for a malignant posterior fossa tumour (PFT) are at risk of intellectual impairment. Cerebellar deficits caused by the tumour and medical procedures, especially radio- and chemotherapy, have a strong impact on intellectual performance. It is worth mentioning that beyond the localisation and volume of the tumour, the crucial factor is also postoperative cognitive dysfunction — POCD) [26]. It has not an official definition, but some authors claim that this consists of cognitive impairment of one or several functions, which results in e.g. attention disorders [7,8], working-memory disorders [9] and lower general IQ [4], occurring past surgical and others medical procedures. It can last from several days to months [27] and can be caused by the damage of neural connections between the cerebellum and encephalon which are responsible for cognitive performance. The group especially vulnerable to long-term effects of treatment in our study are children with an age at diagnosis lower than 8.5, similarly to [28]. Such children have lower verbal abilities, such as immediate memory, focus, word knowledge, and giving the definition of words. Worse functioning could be observed also in performance ability, such as visual-processing speed and short-term visual memory.

In the DWI, DTI, and MRI procedures such anatomical structures as the vermis, foramen of Luschka, and gliosis were examined. Especially, the middle part of the vermis and extension of the foramen of Luschka were of significance. Other features, such as the location of the tumour, did not differentiate the level of cognitive performance in the examined group, in contrast to the previous studies [29, 30]. Differences can be caused by the differences in examination time. Our patients were examined for cognitive performance at a minimum of 3 years after the end of the treatment, whereas Riva [29] made the measurements during the treatment and Puget et al. [30] at least 6 months after the end of the treatment. So, we can assume, at an early stage, that the location of the tumour in the left or right side of the cerebellum can negatively affect cognitive functions but, with the passage of time, children effectively compensate for this decline. To test this hypothesis, a longitudinal study should be conducted, beginning at the end of treatment up to 6–7 years after the end of the treatment, to determine if the compensation effect occurs systematically.

The lack of the foramen of Luschka is so essential for the cognitive functioning of survivors that, even after the passage of time after treatment, it still differentiates patients. This area especially affects the general IQ level, both verbal and nonverbal. The largest difference above one SD appears in nonverbal intelligence, which indicates difficulties in knowledge acquisition. Significant differences were also noted in two subscales (similarities, picture ordering) of verbal intelligence. The key abilities in both these tasks are reasoning and compartmentalization. It is also worth mentioning that the age of the children is correlated with cognitive performance after the end of the treatment: the younger the children, the worse the cognitive performance, especially in verbal intelligence. Younger children (range at surgery: 4–8 years old) had the lowest scores in semantic fluency and, consequently, showed the most difficulty in verbal intelligence.

The second significant area was the middle part of the vermis. Damage of this area concerned younger children (M = 7.72) most often. This relationship can result from the fact that tumour often occurs in the inferior and middle part of the vermis and, in young children, these structures are so small that resection with margins hooks this field. Puget et al. [30] obtained similar results, although they indicated more firmly the inferior part of the vermis

Limitations of the study

The study is a cross-sectional analysis. Our sample size was limited and three subjects did not meet the 3-year-period criterion There is a need to replicate the study in a bigger sample, which will enable subgroup analyses.

The second limitation is that this study is restrained to one country whose sociocultural heritage and quality of healthcare system may have influenced participants' responses, therefore, limiting the generalizability of the results to other nations that differ significantly from Poland for the aforementioned variables.

In addition, the effect of radiation on the cognitive impairment could not be controlled, as the standard procedure assumed a surgical procedure as well as radiotherapy. Thus, the assignment of a control group was ethically impossible.

Clinical implications

The study provides insight into the effect of childhood neoplasm on the cognitive performance of survivors. An accurate assessment of a child's cognitive performance at different stages of treatment and recovery contributes to care planning and matching them with tailored support services.

Based on these results, we suggest that further intervention or qualitative studies explore whether therapeutic interventions directed towards the support of cognitive development could lead to long-term improvement.

Conclusions

Cerebellar damage plays a major role in cognitive impairment in children with posterior fossa tumours. Children with postoperative and persistent cerebellar deficits are at risk for impaired intellectual outcome and deserve special education measures as soon as possible after the completion of cancer treatment. During surgery of younger children (especially below 8), special care during resection should be taken in the area of the middle and inferior part of the vermis, because any damage can cause negative effects difficult to rehabilitate. Evaluating children three years after treatment, however, resulted in improvement in many cognitive functions.

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Conflict of interests

None declared.

Funding

None declared.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval statement

The advice of the Internal Review Board of the Medical University of Silesia in Katowice so as to the need of submitting a formal application for study protocol approval was sought prior to the commencement of this study. The IRB approved the study as a non-interventional one. Reference number for the approval: KNW/022/KB/49/15.

Patient consent statement

Every participant expressed written, informed consent before the beginning of the study.

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