

Perioperative risk factors for long-term intelligence in children with postoperative cerebellar mutism syndrome after medulloblastoma surgery

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Abstract

Objective: Approximately 7%–50% of children with medulloblastoma (MB) develop postoperative cerebellar mutism syndrome (pCMS). pCMS has a short-term negative impact on intelligence, but effects on long-term outcomes are contradictory. The aim of this study was to assess long-term effects of pCMS in MB patients on aspects of intelligence quotient (IQ) and its perioperative risk factors.

Methods: In this single-center retrospective cohort study, 31 children were included (14 pCMS). Perioperative risk factors included brainstem invasion, vermis incision, hydrocephalus, tumor size, severity of pCMS, neurological symptoms, mean body temperature (BT) on days 1–4 post surgery, and age at resection. Age-appropriate Wechsler Intelligence tests were assessed at least 2 years after tumor resection.

Results: Mean interval between tumor resection and neuropsychological evaluation was 3.9 years in pCMS and 4 years and 11 months in the no-pCMS group. No significant differences in IQ scores were found between groups. The pCMS group had a clinically relevant difference of 10 points when compared to age norms on verbal IQ (VIQ). Bilateral pyramidal and swallowing problems were risk factors for lower performance. In the overall group, tumor size, younger age at surgery, and raised mean BT were negatively correlated with aspects of IQ.

Conclusions: We found a clinically significant reduction of VIQ in the pCMS patient group. pCMS patients with a larger tumor size, younger age at surgery, a higher mean BT in the first days after surgery, bilateral pyramidal symptoms, and swallowing problems 10 days post surgery are more at risk for VIQ deficits at long-term.

KEYWORDS

intelligence, IQ, medulloblastoma, mutism, pCMS, pediatric, posterior fossa, postoperative cerebellar mutism syndrome, risk factors, tumor

Abbreviations: BT, body temperature; DTC, dentato-thalamo-cortical; FSIQ, full-scale IQ; IQ, intelligence quotient; M, mean; MB, medulloblastoma; MRI, magnetic resonance imaging; pCMS, postoperative cerebellar mutism syndrome; PIQ, performance IQ; PSI, processing speed index; SCP, superior cerebellar peduncle; SD, standard deviation; VIQ, verbal IQ

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1 | INTRODUCTION

Medulloblastomas (MB) are malignant embryonal neuroepithelial brain tumors located in the posterior fossa. They are common in children and have a prevalence of 9.2% in pediatric brain tumors between the ages 0 and 14 years, with the highest rates between 3–4 and 8–10 years of age.¹

Treatment for MB consists of surgery, followed by chemotherapy and radiation therapy.² Different types and doses of radiation are used, depending on risk classification. The overall 5-year event-free survival rate for patients with MB is 70%.² Five-year event-free survival in average-risk patients (>3 years of age, <1.5 cm² of tumor present after surgery and no metastatic disease) is up to 85%.³ In contrast, children younger than 3 years have an unacceptable risk of severe neurocognitive impairment after radiotherapy and were previously treated without upfront radiotherapy, resulting in a poor 5-year event-free survival.^{4–6} Long-term cognitive and academic performance may be impaired, especially for those who are younger at diagnosis and receive higher doses of radiation.⁶ Reduction of craniospinal radiation dose and efforts to reduce the boost volume could not prevent this effect in young children.⁶ Surgery aims for maximum tumor resection but is not without risks, as 7%–50% patients may develop postoperative cerebellar mutism syndrome (pCMS).^{7–9} According to the consensus between experts associated in the Posterior Fossa Society (<http://www.posteriorfossa.org/>), typical features of pCMS are delayed onset of mutism or severely reduced speech and emotional lability after cerebellar or fourth ventricle tumor surgery in children.⁹ Additional common features include hypotonia and oropharyngeal dysfunction/dysphagia.⁹ It is frequently accompanied by cerebellar motor syndrome and brainstem dysfunction, including long tract signs and cranial neuropathies.⁹ Because the cerebellum also contributes to cognitive functions such as linguistic processing, executive functioning, visual spatial abilities, and affective modulation, symptoms compatible with the cerebellar cognitive affective syndrome (CCAS) may also be present.^{10,11} The mutism or severely reduced speech is always transient, but recovery may be prolonged, speech and language may not return to normal, and other deficits of cognitive, affective, and motor functions often persist.⁹

At relatively short-term (12 months post diagnosis), lower full-scale intelligence quotient (FSIQ) and processing speed index (PSI) were found in 22 pCMS patients compared to a matched control group.¹² In a study of 107 patients with pCMS 1 year post diagnosis, intellectual disabilities were found in 59% of patients with severe pCMS (defined as mutism or severely reduced speech lasting >4 weeks) compared to 17% of patients with moderate pCMS (defined as mutism or severely reduced speech between 1 and 4 weeks).¹³ Compared to children with no pCMS after resection of MB, children with pCMS also exhibited significantly more obsessive-compulsive types of behavior, withdrawal behavior, social problems, and internalizing problems 1–2 years after completion of therapy.¹⁴

Long-term intellectual outcome studies show contradictory results. At a mean of 4.5 years after surgery, a nonsignificant lower intelligence

of 16 points was present in five MB patients with pCMS compared to 12 MB patients without pCMS.¹⁵ In another study, nine children with pCMS had a significantly lower intelligence compared to 67 children without pCMS 2 years after MB diagnosis.¹⁶ In a study of 165 children 3–5 years after diagnosis of MB, a significant decline over time of intellectual and academic performances was observed.¹⁷ However, the performance of the majority of patients remained within the average range at 5 years after diagnosis.¹⁷ Also, serious hearing loss and pCMS independently predicted below-average estimated mean intellectual ability at 5 years post diagnosis, and patients with high-risk MB and young age (<7 years) at diagnosis exhibited the biggest drop.¹⁷ In another study, 36 patients with pCMS and 36 age-matched controls were compared at 1, 3, and 5 years after diagnosis of MB.¹⁸ The pCMS group exhibited estimated mean scores that were at least one standard deviation (SD) below the mean for FSIQ, PSI, broad attention, and working memory across all time points and for 5 years after MB diagnosis.¹⁸ Attention and working memory declined over time.¹⁸ In another long-term follow up study of 121 patients at a mean of 6.1 years after MB diagnosis, 34 identified pCMS patients had a lower total intellectual functioning compared to patients without pCMS.² In 58 adult survivors of childhood MB, FSIQ assessed at a mean of 6.6 years after the end of treatment ranged from 46 to 131.¹⁹ Lower socio-economic status (SES) and presence of pCMS, but not a hearing deficit, had significant negative effect on overall IQ.¹⁹ Of 13 out of 58 patients with pCMS, only one had an overall IQ >80 (most had IQs in well-below average range).¹⁹ The living situations of the patients with pCMS reflected these negative effects on IQ at a mean of 14.9 years after end of treatment. For example, 10 out of 58 were not fully independent for some activities of daily living and had attended specialized schools and 13 were unemployed.¹⁹ These findings contrast with those in a recent long-term follow-up study in patients after MB treatment in which neuropsychological outcome of 18 children with pCMS was compared to matched controls 3 years after diagnosis.²⁰ In the pCMS group, expressive vocabulary and fine motor speed were diminished, but no group differences were found in overall intelligence, receptive vocabulary, visuomotor integration, inhibition, emotional control, depression, and anxiety.²⁰

At present, two prediction tools have been published to predict the occurrence of pCMS, both of which still have to be validated.^{8,21} No prediction tool has yet been published for duration of the mute or severely reduced speech phase of pCMS. The findings of Robertson et al. suggest that mutism or severely reduced speech of >4 weeks duration has a negative effect on intellectual function.¹³ If severe pCMS or long duration of pCMS are negative prognostic factors for intellectual deficits, then perioperative prognostic factors that can be influenced may become critical for predicting intellectual impairment. In both studies in which a prediction tool for development of pCMS was described, damage to the superior cerebellar peduncles (SCP) during surgery was found to be such a contributing risk factor.^{8,21} A 0.5°C higher mean body temperature (BT) in the first 4 postoperative days increased the odds ratio for the development of pCMS almost fivefold.²² The latter risk factor was found to be a major contributor in the

Rotterdam prediction tool for pCMS.⁸ In some studies, children with cerebellar damage are particularly at risk for long-term neuropsychological dysfunction, thus requiring active rehabilitation measures.^{15,16}

The purpose of the present study is to describe the impact of pCMS on intellectual functioning and identify relevant pre- and postoperative risk factors for lower cognitive scores. To account for late effects of radiotherapy, we assessed FSIQ at a mean of 3 years post diagnosis in MB patients with and without pCMS.⁶

2 | MATERIALS AND METHODS

This is a single-center retrospective cohort study in Erasmus MC/Sophia Children's Hospital of patients with MB who were treated between 1992 and 2017 with surgery, chemo- and adjuvant craniospinal radiotherapy and who completed a neuropsychological assessment at least 2 years post diagnosis. Neuropsychological evaluation followed the protocol of the Childhood Oncology Group in the Netherlands. Children treated for a MB complete neuropsychological evaluation 6 months after completion of chemotherapy, as well as 3 and 5 years after tumor resection. Intelligence is included in this protocol and is assessed with the age-appropriated Dutch form of the Wechsler Intelligence Scales (FSIQ, total verbal intelligence [VIQ], total performance intelligence [PIQ], PSI). Data were acquired from the standardized clinical, radiological, and neuropsychological follow-up of brain tumor patients in our multidisciplinary clinical and outpatient setting as documented in the electronic patient record. In order to make a reliable diagnosis of pCMS, children were not included when age at surgery was <2 years. pCMS assessment included a daily postoperative neurological examination and assessment of speech, language, and behavior in the first 2 weeks after surgery.^{23,24} After diagnosis of pCMS, patients were subsequently assessed every second week until the recurrence of speech, language, or normalization of behavior to the premorbid situation as reported by the parents.^{23,24} Following Robertson et al., pCMS was considered severe when the phase with mutism or extremely reduced speech lasted 4 weeks or more.¹³ A pediatric neurologist examined all children at regular intervals to establish residual neurological impairments. Neurologic examination 10 days post surgery was scored systematically and focused on the following domains: (a) swallowing problems: absent or severe (needs tube feeding); (b) pyramidal symptoms: absent, present unilateral, or present bilateral; (c) axial ataxia: absent or mild (can sit/stand without support) versus severe (cannot sit or stand without support); (d) limb ataxia: absent or mild limb ataxia (no functional impairment) versus severe ataxia (through which functional impairment); and (e) oculomotor symptoms: absent, mild (saccadic eye movements and/or first-degree horizontal nystagmus), or severe (second- or third-degree nystagmus). Brain T1, T2, FLAIR magnetic resonance imaging (MRI) images at diagnosis with and without enhancement were reviewed for preoperative size and site of the tumor and brainstem invasion.⁸ We computed the bicaudate index (BI) as a measure of ventricular dilation.⁸ Ventricular dilation was distinguished as none (BI < 0.19),

mild (BI = 0.19–0.26), or severe (BI > 0.26).⁸ Follow-up MRI at the time (± 3 months) of neuropsychological assessments was used to determine the ventricle width and vermis incision.

2.1 | Ethical considerations

According to Dutch law, no approval of a Medical Ethical Committee is needed when patient data are studied that are obtained as part of routine patient care. As is required by Dutch law, parents and patients >12 years old signed a consent form before neuropsychological assessment, in which they allowed the data to be used for research.

2.2 | Statistical analysis

The data of the neuropsychological assessment were compared with the normative data for the Dutch population and corrected for age. FSIQ, VIQ, PIQ, and PSI were compared to the mean IQ scores in the normal population using a one-sample *t*-test. IQ scores were compared between the groups with and without pCMS using an independent sample *t*-test. Before computing the independent sample *t*-test, assumptions of normality of the dependent variables and homogeneity of variance had to be met.²⁵ A post hoc paired sample *t*-test was computed to check differences between VIQ and PIQ within the two groups.

Included risk factors for a lower intelligence in patients with pCMS were brainstem invasion, vermis incision, pre- and postoperative hydrocephalus, tumor size, severity and duration of pCMS, mean BT on days 1–4 post surgery, and age at resection.⁸ These risk factors were analyzed with a two-sided bivariate Kendall's Tau correlation and before computing this analysis, assumptions of normality of the dependent variables had to be met.²⁵ Missing data were deleted pairwise because data were missing randomly. A multiple regression analysis based on backward elimination procedure was conducted. Before computing this regression, assumptions of linearity, multicollinearity, homoscedasticity, normally distributed errors, and independence of the error were checked.²⁵ To analyze data, Statistical Package of Social Science (SPSS) version 25 was used and results were considered statistically significant at a *p*-value of <.05.

3 | RESULTS

Between 1992 and 2017, a consecutive series of 118 children were diagnosed with MB in Erasmus MC/Sophia Children's Hospital. Eighty-seven patients did not meet the inclusion criteria. Forty-nine children died within 2 years after diagnosis. Thirty-one of them were 3 years or younger at surgery and did not receive upfront radiotherapy. Of the 18 children who were older and received upfront radiotherapy, eight were

diagnosed with pCMS. The interval diagnosis assessment was too short in 16 patients. The diagnosis of pCMS was not reliably possible because of age <2 years at surgery in six surviving patients. Five children did not receive adjuvant radiotherapy because of young age. Three children were lost to follow-up. Two patients could not perform the Wechsler intelligence test because of severe visual or auditory deficit. All children had routine follow-up and treatment in a pediatric rehabilitation center and had annual neurologic evaluation at our multidisciplinary neuro-oncological follow-up outpatient clinic. In six children, the neuropsychological evaluation was performed in their rehabilitation center because of a shorter travel distance.

3.1 | Patient characteristics

Demographic characteristics of the 31 patients are listed in Table 1. Fourteen patients developed pCMS with a duration of 4–212 days (mean [*M*] = 45, *SD* = 45 days). Six children had a duration of pCMS symptoms of >4 weeks (duration of pCMS 32, 45, 35, 70, 124, and 212 days), and at least one other symptom classified as severe by Robertson et al.¹³ One of these children classified as pCMS because of a severely reduced speech and severe irritability. Three children were classified as mild pCMS (duration of pCMS 4, 5, and 9 days) and five children as moderate pCMS (duration of pCMS 12, 14, 16, 20, and 21 days) (Table 2, 3). None of the children classified as mild or moderate pCMS experienced reduced speech. The pCMS and no-pCMS groups differed in mean BT within the first 4 days after surgery, but not in age, tumor size, tumor location, hydrocephalus, chemotherapy protocol, radiation dose, or premorbid disorder.

3.2 | Neuropsychological data

Mean age at assessment was 11 years and 11 months and mean follow-up period was 3 years and 9 months in the pCMS group and 11 years and 7 months and 4 years and 11 months, respectively, in the non-pCMS group. There were no significant differences between the pCMS and non-pCMS groups for age at resection, age at assessment, time interval resection and assessment, gender, and number of patients deceased at the moment of writing.

In comparison with the normal population, the whole MB group showed weaker performances on FSIQ, VIQ, PIQ, and PSI (FSIQ $t = -6.742$, $p < .001$; VIQ $t = -4.433$, $p < .0001$; PIQ $t = -8.459$, $p < .0001$; PSI $t = -10.055$, $p < .0001$). No significant differences were found for FSIQ (pCMS group mean 77 ± 16 ; non-pCMS group mean 83 ± 16), VIQ (pCMS group mean 80 ± 1 ; non-pCMS group mean 89 ± 17), PIQ (pCMS group mean 72 ± 15 ; non-pCMS group mean 76 ± 16), and PSI (pCMS group mean 71 ± 15 ; non-pCMS group mean 74 ± 12) between the pCMS and non-pCMS groups. A relevant difference was found on VIQ (89 in non-pCMS group vs. 80 in pCMS group). In the Netherlands, this difference in IQ score is of clinical relevance, at a cutoff score of <85 for getting extra help at school. This 1 SD below the standardized mean score may also be used in other coun-

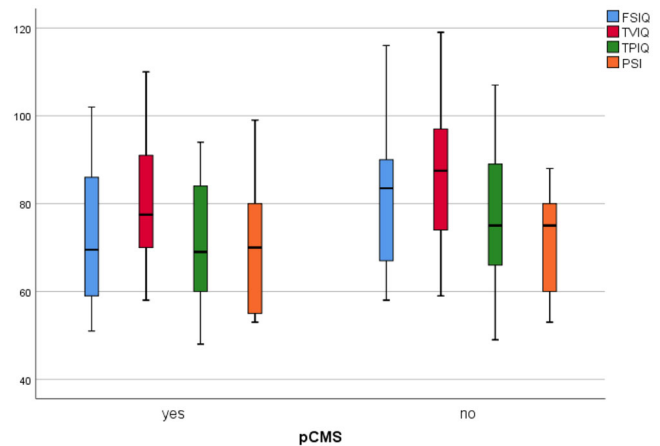


FIGURE 1 IQ scores pCMS versus non-pCMS groups. FSIQ, full-scale intelligence; IQ, intelligence; pCMS, postoperative cerebellar mutism syndrome; PSI, processing speed index; TPIQ, total performance intelligence; TVIQ, total verbal intelligence

tries/states/provinces as a clinically significant cutoff. In the non-pCMS group, only 58% of patients had a VIQ between the range of 85 and 115 (1 SD below and above 100) versus 27% of pCMS (chi-square $p = .105$). All intelligence scores are shown in Figure 1.

3.3 | Risk factors for intelligence in pCMS

In the whole group, lower FSIQ correlated with lower age at resection ($r = .39$, $p = .03$), lower age at assessment ($r = .42$, $p = .02$), and mean raised postoperative temperature ($r = -.41$, $p = .03$). A correlation was found between poorer VIQ and larger tumor size ($r = -.45$, $p < .03$). Poorer PSI was also correlated with mean raised BT ($r = -.42$, $p = .04$) and preoperative hydrocephalus ($r = .48$, $p = .02$).

In the pCMS group, we found correlations between lower FSIQ and greater tumor size ($r = -.59$, $p = .04$) and between lower VIQ and greater tumor size ($r = -.77$, $p < .01$) and higher temperature ($r = -.67$, $p = .02$). We did not find a correlation between duration of pCMS and intelligence scores. However, a mutism duration of more than 15 days in children with pCMS significantly correlated with the presence of severe swallowing problems ($r = .41$, $p < .01$) and severe axial ataxia ($r = .56$, $p < .01$) 10 days after surgery. Swallowing problems and bilateral pyramidal symptoms were also found to be risk factors for long-term VIQ deficits.

Multiple regression analysis (Table 3) showed significant independently related predictors for lower FSIQ, VIQ, and PSI scores: younger age at resection, higher mean BT 1–4 days after surgery, larger tumor, and presence of preoperative hydrocephalus. There were no significant predictors for PIQ.

4 | DISCUSSION

In the present long-term outcome study, MB survivors had significantly lower performance compared to their healthy peers on measures of IQ

TABLE 1 Clinical characteristics

	pCMS Mean (SD)	No pCMS Mean (SD)	p-Value
Patients (number)	14	17	
Sex (male)	64%	65%	.72
Deceased	21%	5%	.24
Age at resection (years, months)	8,4 (3,7)	8,3 (3,4)	.93
Age at assessment (years, months)	11,9 (3,7)	11,7 (3,9)	.85
Interval resection assessment (years, months)	3,9 (2,1)	3,9 (3,0)	.28
Tumor size diameter in cm	4.9 (0.7)	4.6 (0.7)	.20
Tumor location			
Brainstem	71%	60%	.51
Vermis	93%	85%	.50
Hydrocephalus			
Preoperative	86%	75%	.46
Postoperative	57%	45%	.59
Mean temp 1–4 days after resection in °C	37.8 (0.5)	37.3 (0.5)	.005
Treatment protocol			.11
Standard risk	71%	45%	
High risk	7%	10%	
Other	21%	45%	
Radiation dose posterior fossa in Gy (mean, SD)	48.5 (13.9) Range 24–68	53.2 (7.2) Range 31–68	.28
Radiation dose craniospinal in Gy (mean, SD)	30.7 (6.4) Range 23–36	27.4 (6.5) Range 18–40	.25
Disorder presurgery	0%	15%	.89
Duration mutism or severely reduced speech in pCMS days (mean)	4–212 (45)		
Neurologic examination on day 10 after surgery			
Axial ataxia severe	50%	0%	
Limb ataxia severe	50%	29%	
Swallowing problems severe	57%	0%	
Pyramidal symptoms	21%	35%	
Oculomotor symptoms severe	43%	12%	

Abbreviations: °C, degrees Celsius; cm, centimeter; Gy, Gray; pCMS, postoperative cerebellar mutism syndrome; SD, standard deviation.

and processing speed, as can be expected after craniospinal radiation.⁶ In agreement with the studies of Wells et al.¹⁵ and Grieco et al.,²⁰ we found that FSIQ scores in MB patients with pCMS did not significantly differ from those without pCMS. However, a clinically relevant difference was found on VIQ.

There is a general agreement that interruption of the dentato-thalamo-cortical (DTC) pathway is the main cause for pCMS.²⁶ Especially, tumor invasion of or postsurgical damage to the right SCP raises the risk to develop pCMS.^{8,21} The right SCP is the outflow channel of the cerebellum to the eloquent left cerebral hemisphere and lower VIQ may reflect the involvement of the proximal right DTC in pCMS. Our findings contrast those in previous long-term studies, in which intelligence in MB patients with pCMS was significantly lower compared to MB patients without pCMS.^{2,13,16} Several factors may have influ-

enced our results. We included patients with delayed onset of mutism ($n = 13$) or severely reduced speech ($n = 1$) and emotional lability after cerebellar or fourth ventricle tumor surgery thus answering to the definition of pCMS according to the consensus between experts associated in the Posterior Fossa Society.⁹ In previous long-term studies, children with a remainder of speech were excluded.^{2,13,16} We only could include a relatively small number of patients (26% of the cohort) in our study and these survivors may have been the children that were less affected. Delayed recovery of motor initiation and verbalization has been described in pCMS patients.²⁷ These deficiencies influence performance on IQ tasks and may explain the lower intelligence scores in pCMS patients 1 year after surgery but may lose influence on IQ measurements 2–3 years after diagnosis.¹² Because our patients were not neuropsychologically tested within a year after diagnosis, we

TABLE 2 Characteristics of postoperative cerebellar mutism syndrome (pCMS) symptoms

Patient diagnosed with pCMS	Gender (M/F)	Age at surgery (years,months)	Days after surgery before pCMS onset	pCMS characteristics	Duration pCMS (days)	Ataxia (days)	Hypotonia (days)	Irritability (days)	Severity score following Robertson et al. ¹³
1	M	6,11	1	Mutism	5	4	2	3	Mild
2	F	7,11	0	Mutism	20	25	20	15	Moderate
3	M	8,7	0	Mutism	4	10	0	3	Mild
4	F	4,8	0	Mutism	21	27	20	18	Moderate
5	F	8,8	0	Mutism	32	60	45	25	Severe
6	M	17,7	1	Mutism	70	120	120	60	Severe
7	M	6,6	0	Mutism	124	35	25	10	Severe
8	M	12	3	Severely reduced speech	212	100	84	154	Severe
9	M	4,8	2	Mutism	14	16	0	0	Moderate
10	M	11,4	1	Mutism	16	14	14	5	Moderate
11	M	5,3	0	Mutism	45	70	50	40	Severe
12	M	4,8	0	Mutism	35	60	50	30	Severe
13	M	11,7	1	Mutism	12	20	18	0	Moderate
14	F	7,9	0	Mutism	9	5	4	5	Mild

TABLE 3 Significant independently related predictors for lower FSIQ, VIQ, and PSI scores in total group

Intelligence	R ²	p-Value	Predictors	Standardized β coefficients
FSIQ	.35	.01	Age at resection	.35
			Mean body temperature	-.31
			Size of tumor	-.22
VIQ	.31	.04	Age at resection	.34
			Size of tumor	-.25
			Mean body temperature	-.17
PSI	.31	.04	Preoperative hydrocephalus	.37
			Mean body temperature	-.22
			Size of tumor	-.21

Abbreviations: FSIQ, full-scale intelligence; PSI, processing speed index; VIQ, total verbal intelligence.

could not study the development of their performance. A third possibility is that at long-term, the deleterious effect of brain irradiation may be stronger than the effect of pCMS, when initially there might have been a difference in intelligence scores.¹² More recently, Kahalley et al. described relative intellectual sparing after proton radiotherapy in MB patients. However, pCMS emerged as a significant contributor to long-term intellectual function such that a history of pCMS was consistently associated with lower scores across all index scores of FSIQ, verbal comprehension, perceptual reasoning, working memory, and processing speed.²⁸

Risk factors for pCMS that were significant in our study agree with results in earlier studies and include midline location of the tumor,²⁹ brainstem invasion,^{13,29} large tumor size (>5 cm in diameter), and MB.^{24,29} More recently, two risk models were published for the development of pCMS based on preoperative findings.^{8,21} Until now, the effect of these risk factors on long-term intelligence in pCMS patients was not described. In the present study, we found that larger tumor size is correlated with poorer long-term intelligence scores in pCMS patients. A larger tumor may lead to lower intelligence scores because a larger tumor destroys more healthy tissue causing more brain damage.³⁰ Also, a larger resection area increases the risk on additional brain damage leading to lower intellectual functioning.³¹ BT in the first 4 days post surgery differed significantly between the two groups, with a higher mean BT of 0.5°C in MB patients with pCMS. The cause of pCMS is undoubtedly multifactorial.²⁶ Our hypothesis is that a higher postoperative BT leads to metabolic stress and induces secondary oxygen depletion in the surgical area, thus causing secondary neuronal damage that would explain the delayed onset of pCMS.^{22,32} This hypothesis is in line with findings in patients after stroke, in whom hyperthermia is associated with relatively large infarction volumes and poorer outcome, even after adjustment for initial stroke severity.²² Monitoring of BT and rigorous treatment with drugs to lower BT is already standard care in patients with SAH and stroke and may also be an important tool to prevent or at least moderate the cascade of events that lead to the development of pCMS.²² The influence of a relatively raised BT after surgery is also in agreement with the hypothesis that heat injury through perioperative use of CUSA mimics the selec-

tive damage caused in heat stroke in which cerebellar structures are selectively vulnerable.³³ Our finding of a correlation between higher postoperative mean BT during the first 4 days and lower IQ may indirectly support the long-term negative influence of pCMS on intellectual functioning.

In agreement with Korah et al., we found that FSIQ correlated with age at resection ($r = .39, p = .03$) and age at assessment ($r = .42, p = .02$) and confirms their observation that a younger age at surgery is a risk factor for development of pCMS.³⁴ Acquired brain injury has a negative impact on the development of the brain.³⁰ For example, also in children with traumatic brain injury, a linear relationship of age at injury and neurological outcome has been demonstrated.³¹

In line with findings by Palmer et al., differences in IQ scores between patients with and without pCMS were significant after controlling for brainstem invasion, but we did not find brainstem invasion to be an influential factor for IQ scores.¹² In contrast with the findings of Robertson et al. who reported that a longer duration of pCMS led to more global intellectual disabilities, the duration of pCMS did not influence intelligence scores in this study also not after confounding for the one patient with pCMS and severely reduced speech.¹³ This bias may be explained by a difference in study populations with approximately 65% of MB patients with moderate-to-severe pCMS in our study versus 92% in the study of Robertson et al.¹³

When children develop pCMS, the duration of the mute phase is often hard to predict. For parents, this is however one of the most important issues. We found a positive significant correlation of pCMS duration of more than 15 days with presence of severe swallowing problems (child is in need of tube feeding) and presence of severe axial ataxia (needs support with sitting and standing) 10 days after surgery. In contrast, we did not find severe axial ataxia a risk factor for lower IQ scores in pCMS patients. Our finding that swallowing problems and bilateral pyramidal symptoms were risk factors for a lower VIQ may reflect the long-term impact of bilateral anterior opercular dysfunction in the context of pCMS. Anterior opercular lesions may cause the perisylvian syndrome, which is a rare type of suprabulbar palsy with key symptoms of bilateral central voluntary paresis of the lower cranial nerves and severe dysarthria or anarthria and swallowing

problems.³⁵ It may be accompanied by bilateral pyramidal symptoms. It has been reported in patients with central nervous system infections, stroke or tumor invasion in the anterior opercular regions on both sides.³⁵

Methodological strengths of this study are that we divided intelligence scores in four different domains, and results reflect the specific influence of pCMS on VIQ. Also, intelligence was assessed at least 2 years since diagnosis with a mean of 3 years post surgery, thereby taking late effects of radiotherapy into account. A weakness was the small sample size because many patients died before long-term comprehensive neuropsychological evaluation, thus reflecting the poor prognosis of the disease and taking into account that patients that could be included in this study were treated according to the MB protocols in use at that time. This also illustrates the need of international studies such as the Nordic study on the consequences of pCMS in children with posterior fossa tumors that can include a large number of patients within a limited timeframe.³⁵ The results of our study emphasize the importance of longitudinal studies that aim to monitor the development of intelligence in the first 2 years after pCMS. This will likely be best conducted in a larger population to give more insight into the relationship between intelligence and pCMS; one such example is the ongoing study in northern European countries.³⁶

5 | CONCLUSIONS

The survivors of MB with and without pCMS showed significant reduction on measures of IQ and processing speed more than 2 years after diagnosis in comparison to healthy peers. Clinically relevant differences in VIQ were found between the group with and without pCMS. Risk factors in pCMS patients that contribute to clinically relevant lower IQ scores included larger tumor size, younger age at surgery, and higher mean BT during the first 4 days post surgery. Children with a moderate or severe form of pCMS, bilateral pyramidal symptoms, and severe swallowing problems on day 10 after surgery are more at risk for long-term VIQ deficits. Surgical guidelines that minimize risks for pCMS while maintaining survival should be further explored. Examples include reducing surgery-related risk factors for pCMS, such as sparing SCP through a delicate approach during tumor surgery and active control of postoperative BT.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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