Risk factors for development of postoperative cerebellar mutism syndrome in children after medulloblastoma surgery

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OBJECTIVE Postoperative cerebellar mutism syndrome (pCMS) occurs in 7%–50% of children after cerebellar tumor surgery. Typical features include a latent onset of 1–2 days after surgery, transient mutism, emotional lability, and a wide variety of motor and neurobehavioral abnormalities. Sequelae of this syndrome usually persist long term. The principal causal factor is bilateral surgical damage (regardless of tumor location) to any component of the proximal efferent cerebellar pathway, which leads to temporary dysfunction of cerebral cortical regions as a result of diaschisis. Tumor type, cerebellar midline location, and brainstem involvement are risk factors for pCMS that have been identified repeatedly, but they do not explain its latent onset. Ambiguous or negative results for other factors, such as hydrocephalus, postoperative meningitis, length of vermian incision, and tumor size, have been reached. The aim of this study was to identify perioperative clinical, radiological, and laboratory factors that also increase risk for the development of pCMS. The focus was on factors that might explain the delayed onset of pCMS and thus might provide a time window for taking precautionary measures to prevent pCMS or reduce its severity. The study was focused specifically on children who had undergone surgery for medulloblastoma.

METHODS In this single-center retrospective cohort study, the authors included 71 children with medulloblastoma, 28 of whom developed pCMS after primary resection. Clinical and laboratory data were collected prospectively and analyzed systematically. Variables were included for univariate and multivariate analysis.

RESULTS Univariate regression analysis revealed 7 variables that had a significant influence on pCMS onset, namely, tumor size, maximum tumor diameter > 5 cm, tumor infiltration or compression of the brainstem, significantly larger decreases in hemoglobin ($p = 0.010$) and hematocrit ($p = 0.003$) in the pCMS group after surgery than in the no-pCMS group, significantly more reported incidents of severe bleeding in the tumor bed during surgery in the pCMS group, preoperative hydrocephalus, and a mean body temperature rise of 0.5°C in the first 4 days after surgery in the pCMS group. Multiple regression analysis revealed that tumor size, tumor infiltration into or compression of the brainstem, and higher mean body temperature in the first 4 postoperative days were independent and highly significant predictors for pCMS.

CONCLUSIONS The authors confirmed earlier findings that tumor-associated preoperative conditions, such as a maximum tumor diameter ≥ 5 cm and infiltration into or compression of the brainstem, are associated with a higher risk for the development of pCMS. Most importantly, the authors found that a 0.5°C higher mean body temperature in the first 4 postoperative days increased the odds ratio for the development of pCMS almost 5-fold. These data suggest that an important focus for the prevention of pCMS in children who have undergone medulloblastoma surgery might be rigorous maintenance of normothermia as standard care after surgery.

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KEY WORDS postoperative cerebellar mutism syndrome; medulloblastoma; risk factors; prevention; hyperthermia; pediatric; oncology

ABBREVIATIONS BI = bicaudate index; BMI = body mass index; BP = blood pressure; Hb = hemoglobin; HR = heart rate; Ht = hematocrit; pCMS = postoperative cerebellar mutism syndrome.

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POSTOPERATIVE cerebellar mutism syndrome (pCMS) is a common complication of cerebellar tumor surgery in children, with an incidence that ranges from 7% to 50%.³⁵ According to a recently published consensus between experts associated with the Posterior Fossa Society, typical features of pCMS are delayed onset of mutism or severely reduced speech and emotional lability, along with additional common features such as hypotonia and oropharyngeal dysfunction or dysphagia.¹² pCMS is frequently accompanied by cerebellar motor syndrome, cerebellar cognitive affective syndrome, brainstem dysfunction including long-tract signs, and cranial neuropathies.^{4,5,8,12,37,40} The mutism can last 1 day to 6 months.^{12,32} Although symptoms of pCMS were first thought to be transient, long-term follow-up studies found that speech rarely normalizes and that dysarthria and cognitive deficits tend to persist.^{1,15,16,40} One year after medulloblastoma surgery, patients with pCMS have significantly lower academic performance than those who do not develop pCMS after medulloblastoma surgery.^{29,44}

pCMS usually develops after a brief interval of several days of relatively normal speech. This characteristic interval between surgery and onset of symptoms and the potential for reversibility strongly suggest that pCMS is caused not only by the direct surgical injury.²⁴ The principal causal factor is bilateral surgical damage (regardless of tumor location) to any component of the proximal efferent cerebellar pathway (pECP), which leads to temporary dysfunction of cerebral cortical regions as a result of diaschisis.^{5,31} Although the specific pathophysiological mechanism involved is unclear, secondary processes initiated by the tumor resection seem to play a role in completing the bilateral impairment of the pECP. Dynamic perfusional disturbances, edema, transient disturbances in neurotransmitter release, and axonal injury caused by per-operative release of the tumor's compressive force, which leads to a change in local structures and distortion of the architecture of axons, neurofilaments, and intra-axonal organelles, causing injury and dysfunction, have been proposed.^{13,24} Some authors have suggested that vasospasm of vessels supplying the deep cerebellar nuclei and the proximal parts of the cerebello-thalamic fibers might lead to focal and partly reversible hypoperfusion and ischemia,^{5,10,25} which might explain the delayed onset, the type of disturbance, and the resolution after a variable length of time.^{13,20}

Results of previous studies that investigated risk factors for pCMS are somewhat controversial.^{13,35,44} Known risk factors are tumor type (medulloblastoma), tumor location in the vermis, and tumor that invades the brainstem. Risk factors shown in multiple studies to not be associated with pCMS are postoperative CNS infection, aseptic meningitis,^{37,45} and sex.^{6,37} Conflicting results were reported for tumor size,^{6,33} vermal incision,⁶ degree of resection or presence of residual tumor,^{32,45} preoperative and/or postoperative hydrocephalus,^{6,9} edema in various locations (e.g., mesencephalon, cerebellar nuclei, brainstem),^{6,33,37} and age at diagnosis.^{6,19,37}

Until now, there have been no effective preventive measures for reducing the risk of pCMS after cerebellar tumor surgery and no treatment that facilitates recovery from pCMS.^{5,13} In combination with the severity of the

long-term sequelae, this highlights the importance of discovering risk factors in the perioperative period that can be influenced, and thus reduce the risk of development of pCMS.

The aim of this study was to identify perioperative clinical, radiological, and laboratory factors that increase the risk for patients to develop pCMS and focus on those for which precautionary measures to prevent pCMS or reduce its severity might be developed. We specifically examined factors such as temperature, low hemoglobin (Hb) level, low oxygen saturation, and hypotension, which might lead to additional hypoxic-ischemic damage or increased oxidative stress. Surgical removal of a medulloblastoma has been found to be a major risk factor for pCMS.^{6,13,20,21,28,32} Because children with medulloblastoma also form a rather uniform group in terms of location of their tumor, this study focused specifically on children who underwent surgery for this tumor type.

Methods

This was a single-center retrospective cohort study of clinical, radiological, and laboratory data obtained in children who underwent surgery for medulloblastoma between 1992 and 2015. Data were collected systematically and prospectively from paper or digital patient records.

Patient Selection

Primary inclusion criteria for this study were having undergone surgery for a medulloblastoma and an age of 2–18 years. Younger children were excluded, because mutism or reduction of speech is difficult to diagnose when speech is not or not yet fully developed. Seventy-one of 79 children who underwent resection of a medulloblastoma in the Erasmus Medical Center/Sophia Children's Hospital met the inclusion criteria. All children were assessed according to a standard follow-up protocol described earlier⁵ to identify those children who developed pCMS. After surgery, 28 (35%) of these children developed pCMS.

Magnetic Resonance Imaging

Preoperative cerebral MR images (T1-weighted images with and without Gd enhancement, T2-weighted and FLAIR images) were analyzed to determine ventricular size, maximum tumor diameter on sagittal images, and infiltration into or compression of the brainstem, for which compression and tumor invasion could not be conclusively differentiated (Fig. 1). We computed the bicaudate index (BI) as a measure of ventricular dilation.⁶ Ventricular dilation was distinguished as none (BI < 0.19), mild (BI 0.19–0.26), or severe (BI > 0.26).⁶ The presence or absence of stroke in the territory of one of the cerebellar arteries was analyzed on postoperative cerebral MR images (T1-weighted images with and without Gd enhancement, T2-weighted and FLAIR images, and diffusion-weighted images) obtained within 48 hours after surgery.

Laboratory Blood Values

Preoperative and postoperative hemoglobin (Hb) and hematocrit (Ht) values were collected. The last available

FIG. 1. Preoperative sagittal (A1, B1, and C1) and axial Gd-enhanced (A2, B2, and C2) T1-weighted MR images of a patient without pCMS (Patient A) and patients with pCMS (Patients B and C), which are attributed to the group without (A1 and A2) and the group with (B1, B2, C1, and C2) severe compression or possible infiltration of tumor in the brainstem. Possible infiltration of tumor in the brainstem is visible in image B1 (white arrow).

data before and the first available data after surgery were used, with cutoffs of 1 week before and 1 week after surgery. The differences between preoperative and postoperative Hb and Ht values were calculated. Preoperative and postoperative thrombocyte and sodium values and postoperative glucose values were collected also.

Surgical Reports

Data extracted from surgical reports were duration of surgery and the bleeding events that apparently were severe enough to be documented.

Vital Parameters and Fluid Balance During Surgery

Data on length and weight at surgery were collected, and body mass index (BMI) was calculated. Data on blood pressure (BP), central venous pressure, heart rate (HR), and oxygen saturation were also collected. Limits for bradycardia and tachycardia depend on age and were defined as 95–140 beats/minute in children aged 2–5 years, 80–120 beats/minute in children aged 5–12 years, and 60–120 beats/minute in children older than 12 years.

The lowest and highest values for each parameter were collected. If data concerning mean arterial pressure (MAP) were not available, then MAP was estimated using diastolic BP (DBP), systolic BP (SBP), and HR at time of measurement. We used the formula $MAP = DBP + [0.33 + (HR \times 0.33 + [HR \times 0.0012])] \times (SBP - DBP)$.³⁴

Data concerning fluid balance, including volume of blood loss, blood transfusion, and total volume of liquid infusions, were extracted from anesthetic reports. Circulatory volume was estimated by multiplying the weight of the child by 0.8. Except for circulatory volume, all volumes were analyzed in ml/kg of body weight.

Body Temperature After Surgery

The highest measured body temperature on Days 1–4 after surgery (expressed in degrees Celsius [°C]) was collected, and mean body temperature over these 4 days was calculated.

Statistical Analysis

Collected data were analyzed using the statistical computer program IBM SPSS 21.0.0.1. The chi-square test was used to investigate the relation between categorical variables and pCMS. When the expected values that result from the chi-square test were low, Fisher's exact test was used. Nonparametric variables were analyzed using the Mann-Whitney U-test or Spearman rank correlation, and parametric variables were analyzed using the Student t-test. The end point of this study was the incidence of pCMS. First, univariate linear regression analysis was performed to identify parameters that predict the presence of pCMS. Variables that were found to be significant predictors for the incidence of pCMS were added together in a multivariate backward stepwise linear regression model. Multicollinearity was evaluated. Statistical significance was set at a p value < 0.05.

Results

Patient Selection

At group level, there were no differences in sex ($\chi^2 = 0.233$; $p = 0.630$), age at surgery ($F_{[1,69]} = 2.038$; $p = 0.158$), or BMI ($F_{[1,69]} = 0.266$; $p = 0.608$) between children with and those without pCMS after resection of medulloblastoma (Table 1).

Magnetic Resonance Imaging

Preoperative axial and sagittal MR images were available for 55 patients (21 with pCMS and 34 without pCMS). Coronal MR images were available for 43 patients (18 with pCMS and 25 without pCMS). Postoperative images were available for 25 patients with pCMS and 37 without pCMS. Sixteen patients who underwent surgery in the 1990s or in the era preceding digital storage of radiological images had only preoperative and postoperative CT scans available and essential MR images were missing from their files. We found no significant differences in sex, age, BMI, blood values, bleeding events, duration of surgery, vital parameters, or body temperature between children with and those without MR images available.

TABLE 1. Patient characteristics

Characteristic	Patients w/ pCMS (n = 28)	Patients w/o pCMS (n = 43)	p Value
Total study population (%)	39.4	60.6	
Sex (% male)	63.33	71.43	0.630
Age at op (yrs)			0.158
Mean (SD)	9.10 (3.96)	7.58 (4.63)	
Range	3.44–17.77	2.07–17.42	
BMI (mg/kg ²)			0.608
Mean (SD)	16.37 (2.96)	16.00 (2.86)	
Range	12.07–26.18	11.37–24.90	

Of the patients with pCMS, 38% had a maximum tumor size that exceeded 5.0 cm on sagittal MR images compared with 3% of the patients without pCMS ($p = 0.001$, Fisher's exact test) (Table 2). Significantly larger preoperative ventricular dilation ($p = 0.032$) was found in the group with pCMS. Infiltration into or compression of the brainstem ($p = 0.004$) was also significantly more frequent in the pCMS group (Table 2). On postoperative MR images, no difference in the occurrence of posterior inferior cerebellar artery stroke between the groups ($p = 0.096$) was found.

Laboratory Blood Values

In the pCMS group, preoperative and postoperative Hb and Ht values were within their reference range. However, in the pCMS group, significantly larger decreases in Hb ($p = 0.010$) and Ht ($p = 0.003$) were found after surgery than those in the no-pCMS group (Table 2). No significant abnormalities or differences in the other laboratory parameters between the 2 groups were found.

Surgical Reports

A bleeding event at the tumor site during surgery was documented more often in the surgery reports for the pCMS group than in the surgery reports for the no-pCMS group ($\chi^2 = 4.066$; $p = 0.044$). The duration of surgery did not differ between the 2 groups ($p = 0.108$) (Table 2).

Vital Parameters and Fluid Balance During Surgery

None of the analyzed vital parameters or fluid balance parameters differed significantly between both groups. The number of patients in each age group who experienced bradycardia or tachycardia was too small for us to subsequently perform a reliable analysis of maximum values and duration.

Body Temperature After Surgery

The group of patients with pCMS had a significantly higher mean body temperature on Days 1–4 after surgery ($p = 0.01$). In the pCMS group, temperature data from 21 patients in the first 4 consecutive postoperative days were available. In 4 (19%) patients, antibiotics were started in this period because of suspected or proven infection. Of the 37 patients for whom these data were available and who did not develop pCMS, 7 (19%) had positive infection parameters and were started on antibiotics.

Factors Influencing the Incidence of pCMS

Univariate regression analysis identified 7 variables that were significantly related to pCMS, namely, tumor size, maximum tumor diameter, infiltration into or compression of the brainstem, severe preoperative hydrocephalus, Hb and Ht decreases before and after surgery, increased number of documented bleeding events during surgery, and a higher postoperative mean body temperature in the first 4 days after surgery. When multicollinearity was evaluated, multiple regression analysis revealed that tumor size and higher mean body temperature, but not the other significant variables from the univariate analysis, were significant predictors of pCMS outcome (Table 3).

Discussion

The aim of this study was to identify risk factors for pCMS in children who are undergoing surgery for a medulloblastoma to find a possible window for intervention and thus prevent this disastrous postoperative complication. To our knowledge, this is the first systematic study in which perioperative risk factors, including fluid balance, vital parameters, radiological parameters, and laboratory

TABLE 2. Significant parameters between patients with and those without pCMS

Parameter	Patients w/ pCMS (n = 28)*	Patients w/o pCMS (n = 43)*	p Value
Sagittal MR images			
Tumor size >50 mm (no. [%])	8 (38) ²¹	1 (3) ³⁴	0.001
Max tumor diameter in mm (mean [SD])	46.55 (7.17) ²¹	40.46 (6.71) ³⁴	0.002
Tumor infiltration into or compression of brainstem (no. [%])	19 (91) ²¹	18 (53) ³⁴	0.004
Preop BI (mean [SD])	0.22 (0.04) ²⁷	0.19 (0.06) ³⁶	0.032
Hemostatic events noted in op report (no. [%])	9 (35) ²⁶	6 (14) ⁴³	0.044
Laboratory blood values (mean [SD])			
Hb difference pre- & postop (mmol/L)	−1.65 (0.83) ²⁸	−1.03 (1.04) ⁴³	0.010
Ht difference pre- & postop (L/L)	−0.08 (0.04) ²⁸	−0.05 (0.05) ³⁸	0.003
Temp in °C, Days 1–4 (mean [SD])	37.71 (0.34) ²¹	37.20 (1.59) ³⁷	0.01

Temp = temperature.

* Superscript numbers indicate the number of patients with available data.

TABLE 3. Significant predictors for onset of pCMS according to multivariate regression analysis

R ²	p Value	Predictor	Unstandardized β Coefficient	Odds Ratio
0.45	<0.001	Tumor size	0.23	1.26
		Mean temp*	1.60	4.97

R² = coefficient of determination.

* Mean body temperature for postoperative Days 1–4.

blood values, were systematically studied as possible contributing risk factors for pCMS.

We confirm earlier findings that medulloblastomas with a largest diameter of 5 cm or more and tumor invading or compressing the brainstem are major risk factors for the development of pCMS.^{6,13,19–21,24,32,35,37,45} A large tumor that expands into the fourth ventricle can cause damage to the dentate-thalamic tract by invasion or compression of the brainstem or the cerebellar peduncles.^{6,26} Larger preoperative ventricular size^{6,9,19,35,45} occurred significantly more frequently in the pCMS group. However, univariate regression analysis revealed that this risk factor was not independent but instead related to tumor size.

We did not find an age effect in our study, because ages in the pCMS and no-pCMS groups did not differ; this result might be explained by our exclusion of children younger than 2 years because speech is often not or not yet fully developed at this age.

The delayed onset of pCMS argues against surgery as the only factor that contributes to its onset. A major new finding in our study is that a mean body temperature rise of 0.5°C in the first 4 days after surgery increased the risk for developing pCMS almost 5-fold. The raised temperature was not explained in the pCMS group by more infections. Neurons have a high metabolic rate and require more energy than glial cells.¹⁷ The metabolic rate decreases under anesthesia,²³ and when anesthesia wears off, global cerebral oxygen consumption increases again. A higher mean body temperature in the first few postoperative days might increase metabolic stress to such an extent that the oxygen requirements in the area of surgery are met insufficiently, especially when the brain tissue surrounding the site of surgery is in an already critical metabolic status. Our findings are 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.^{11,36,38,40}

Additional analysis of the data by means of a Spearman rank correlation test revealed a strong correlation between total volume of fluid infusions and mean body temperature on postoperative Days 1–4 ($r = 0.512$; $p < 0.0001$) and between the total amount of blood loss and mean body temperature ($r = 0.28$; $p = 0.04$). At a group level, patients with pCMS suffered significantly more incidents of bleeding events severe enough to be documented in the surgical reports than did patients who did not have pCMS. The volumes of plasma infusions were evidently sufficient to secure circulation, because vital parameters remained stable during surgery and did not differ between groups. According to the penumbra concept, the 2 criti-

cal levels of decreased cerebral blood flow are the flow threshold for reversible functional failure (i.e., the penumbra) and a lower threshold below which brain tissue becomes irreversibly infarcted.¹⁴ A decrease of blood flow below the threshold of maintaining neuronal functioning leads to reduced neuronal transmission and in patients with pCMS can induce cerebellocerebral diaschisis. This result is in line with those of SPECT studies that showed hypometabolism reflecting reduced perfusion in different areas of the cerebral hemispheres but more severely in the cerebellar midline of patients with pCMS than in patients without pCMS.^{5,10} However, the bleeding incidents might have been enough to critically impair blood flow around the site of surgery.

pCMS typically is a pediatric syndrome, and only few adults with this condition have been described.³⁵ The reason for this difference might be that in comparison with adults, children have a smaller intravascular volume and are therefore more vulnerable to hypovolemia, which means that even a relatively small amount of blood loss can lead to a deficit in oxygen delivery and induce local ischemia in the surgical area and the immediately adjacent tissues, including the deep cerebellar nuclei on both sides.³⁰ In the pCMS group, the larger number of bleeding incidents with possibly relatively more leakage in the spinal fluid despite preventive measures taken by the surgeon might be the cause of increased metabolic stress caused by a physiological reaction similar to that in patients with subarachnoid hemorrhage (SAH) that contributes to an increased size of the penumbra in the surgical area in patients with pCMS. In patients after SAH, a systemic inflammatory response syndrome (SIRS) is seen commonly independent of infection.⁴¹ The SIRS is associated with hyperthermia in the acute phase and is associated with the development of vasospasms and poor outcome.^{27,42} A raised mean body temperature predicted a poor outcome (odds ratio 31.6 per 1°C) in patients with SIRS.⁴⁴ Induced normothermia in patients with SAH improves outcomes.² In patients with stroke, it was found that each 1°C increase in body temperature leads to a rise in relative risk of poor outcome by 2.2.^{7,36,38} The higher postoperative body temperature in patients with pCMS was clearly a major risk factor (odds ratio 4.97) for the development of pCMS. Monitoring of body temperature and rigorous treatment with drugs to lower body temperature is already standard care in patients with SAH and stroke.^{18,43} We suggest that such methods should also be implemented for patients undergoing resection of a posterior fossa tumor.

Based on our findings, we suggest intensifying measures that prevent extensive bleeding during surgery and excessive leakage of blood in CSF spaces. Antifibrinolytic drugs could be considered to reduce blood loss during surgery.³ Their value was demonstrated already in children undergoing major craniofacial surgery.⁷ Another option that could be explored further is the use of sevoflurane, an anesthetic that is also applicable in children.^{22,39} It has been shown to increase tolerance to lower levels of cerebral blood flow in adult patients undergoing carotid endarterectomy and to decrease infarction size and improve neurological outcome when given before an ischemic event in animal studies.¹⁷

Because our study was of an exploratory nature, some

caution should be taken when interpreting the results. We conducted a retrospective study, which means that confirmation bias cannot be excluded, especially for data collected from MRI, because the MRI evaluations were not blinded. However, confirmation bias did not apply to laboratory and temperature values, data obtained from surgical reports, or data obtained from anesthetic reports, which included fluid balance and vital parameters. These data were collected prospectively as part of standard patient care.

Conclusions

Our results support earlier findings in children with medulloblastoma in which tumor-associated preoperative conditions such as a tumor diameter of 5 cm or more and infiltration into or compression of the brainstem were found to be associated with a higher risk of developing pCMS. An important finding in this study is that children with pCMS had a higher mean body temperature in the first 4 postoperative days, independent from postoperative infections. A 0.5°C higher mean body temperature in the first 4 postoperative days increased the odds ratio for development of pCMS almost 5-fold. We suggest that an important focus for the prevention of pCMS in children who undergo medulloblastoma surgery might be to rigorously maintain normothermia as standard care after surgery. Multicenter studies of the effect of such a regimen on the prevention of pCMS should be performed.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Catsman-Berrevoets, Aarsen. Acquisition of data: Catsman-Berrevoets, Pols, van Veelen, Gonzalez Candel. Analysis and interpretation of data: all authors. Drafting the article: Catsman-Berrevoets, Pols, van Veelen, Aarsen. Critically revising the article: all authors. Reviewed submitted version of manuscript: Catsman-Berrevoets, Pols, van Veelen. Approved the final version of the manuscript on behalf of all authors: Catsman-Berrevoets. Statistical analysis: Catsman-Berrevoets, Pols, van Veelen, Aarsen. Administrative/technical/material support: Gonzalez Candel. Study supervision: Catsman-Berrevoets, van Veelen, Aarsen.

Supplemental Information

Previous Presentations

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