J Neurooncol (2017) 133:539–552
DOI 10.1007/s11060-017-2462-4

CLINICAL STUDY

Analysis of surgical and MRI factors associated with cerebellar mutism

Anjali Sergeant[1] · Michelle Masayo Kameda-Smith[1,2,3,4] · Branavan Manoranjan[1,3,4] · Brij Karmur[1] · JoAnn Duckworth[5] · Tina Petrelli[1,2] · Katey Savage[6] · Olufemi Ajani[1,2] · Blake Yarascavitch[1,2] · M. Constantine Samaan[1,7] · Katrin Scheinemann[1,5] · Cheryl Alyman[1,8] · Saleh Almenawer[1,2] · Forough Farrokhyar[1,6] · Adam J. Fleming[1,5] · Sheila Kumari Singh[1,2,3,4] · Nina Stein[1,9]

Received: 3 September 2016 / Accepted: 6 May 2017 / Published online: 19 May 2017

Abstract The surgical risk factors and neuro-imaging characteristics associated with cerebellar mutism (CM) remain unclear and require further investigation. Therefore, we aimed to examine surgical and MRI findings associated with CM in children following posterior fossa tumor resection. Using our data registry, we retrospectively collected data from pediatric patients who acquired CM and were matched based on age and pathology type with individuals who did not acquire CM after posterior fossa surgery. The strength of association between surgical and MRI variables and CM were examined using odds ratios (ORs) and corresponding 95% confidence intervals (CIs). A total of 22 patients (11 with and 11 without CM) were included. Medulloblastoma was the most common pathology among CM patients (91%); the remaining 9% were diagnosed with a pilocytic astrocytoma. Tumor attachment to the floor of the fourth ventricle (OR 6; 95% CI 0.7–276), calcification/hemosiderin deposition (OR 7; 95% CI 0.9–315.5), and post-operative peri-ventricular ischemia on MRI (OR 5; 95% CI 0.5–236.5) were found to have the highest measures of association with CM. Our results may suggest that tumor attachment to the floor of the fourth ventricle, pathological calcification, and post-operative ischemia have a relatively higher prevalence in patients with CM. Collectively, our work calls for a larger multi-institutional cohort study of CM patients to encourage further investigation of the determinants and management of CM in order to potentially minimize its development and predict onset.

Keywords Cerebellar mutism · Posterior fossa syndrome · Medulloblastoma · Posterior fossa · Fourth ventricle · Brain tumor

Sheila Kumari Singh and Nina Stein are co-senior authors.

✉ Sheila Kumari Singh
ssingh@mcmaster.ca

1 McMaster Pediatric Brain Tumor Study Group, McMaster University, Hamilton, Canada

2 Department of Surgery, Division of Neurosurgery, McMaster University, Hamilton, Canada

3 Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, Canada

4 Stem Cell and Cancer Institute, McMaster University, Hamilton, Canada

5 Department of Paediatrics, Division of Hematology and Oncology, McMaster University, Hamilton, Canada

6 Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada

7 Department of Internal Medicine, Division of Pediatric Endocrinology, McMaster University, Hamilton, Canada

8 Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Canada

9 Department of Radiology, McMaster University, Hamilton, Canada

Introduction

Cerebellar mutism (CM) is a condition characterized by a significant lack of speech or loss of speech in children following posterior fossa (PF) surgery [1]. The definition of CM in relation to Posterior Fossa Syndrome (PFS) is not consolidated in the literature [1]. We chose to define CM as a condition that is part of a larger constellation of symptoms which often involve ataxia, mood changes, and impaired swallowing and vision [1–4]. CM is acquired within 1 week following PF surgery and has a limited duration of weeks to months [5]. However, those affected may

experience long-term effects including dysarthria, altered prosody of speech, and neurological imparments [3, 5].

The biological origin of CM remains largely unclear and there are no standardized treatments. The incidence of CM in children ranges from 8 to 39% of children following PF surgery [6]. The risk of CM has been reported to increase based on medulloblastoma tumor type, or brainstem or vermis invasion [1]. The condition may be triggered by the disruption of the dentato-thalamo-cortical (DTC) pathway during surgery, but an evidence-based proof of CM's etiology has not been described [5, 6].

We sought to determine whether there are any surgical or MRI markers associated with CM in children after PF surgery for tumor resection. We aim to identify trends in the anatomical location of tumor at presentation, MRI features, and the amount of residual tumor in order to understand the pathophysiological factors leading to CM.

Methods

Following local ethics board approval, we conducted a retrospective cohort-comparative study among children diagnosed with PF brain tumors between 2003 and 2015 at McMaster University Medical Centre (MUMC), a pediatric and academic hospital in Ontario, Canada. Data were extracted from the Pediatric Brain Tumor Study Group (PBTSG) database, which compiles information from patient charts and McMaster's Medical Records system. The database was compiled in 2015 to document the brain tumors of children up to 18 years old. Patients who presented to MUMC prior to 2002 were not included due to a lack of accessible MRI data and accessible physician's notes. Double data entry was performed on 5% of the cases to verify the accuracy of data entry.

The senior author's anecdotal clinical experiences noted that children who developed CM post-operatively often had notable intraoperative events (i.e. disruption of the floor of the fourth ventricle leading to changes in vital signs). This led to our hypothesis that significant intraoperative events may lead to post-operative MRI changes which may be predictive of CM. Study protocol was created a-priori; the patient population was defined in advance. CM was defined as a significant lack of speech or loss of speech acquired within 3 days post-operatively. The patients who acquired CM post-operatively (after their first surgery) were matched with patients who did not acquire this condition after the surgical removal of their brain tumor. Cases and controls were matched based on age and tumor type as closely as possible and the review was blinded to outcome, allowing the matching to be performed in an unbiased manner. When there were multiple controls to be matched for one case, one was randomly chosen. All patients included had tumors in the midline or cerebellar hemisphere region. The cases and comparisons extracted for this study were re-examined, and double data entry was performed for 100% of the study's patients.

In addition to the data collected from the PBTSG database, pre-operative and post-operative MRIs of CM patients and their comparisons were reviewed by a single blinded neuro-radiologist. Variables recorded from the pre-operative scans included anatomical tumor location, size of lesion, MRI appearance, T1 turbo spin echo signal, T2 turbo spin echo signal, restricted diffusion, FLAIR signal, presence of metastasis, pattern of enhancement, leptomeningeal enhancement, calcification, necrosis, hydrocephalus, and vasogenic edema. Post-operative variables included residual tumor on MRI, extent of surgical resection, and peri-ventricular infarcts or bleeds around the fourth ventricle. A gross total resection (GTR) was defined as a residual tumor of less than 1.5 cubic centimeters [7]. Data were compared with original MRI scan reports in order to ensure consistency and accuracy, and the anatomical location variable was checked against operative reports. Variables were selected based upon expert opinion and a literature review; the study sought to include variables which had not been previously linked to the occurrence of CM. For data analysis, we reported the mean age with standard deviation (SD) and ratio of male to female in matched cases and comparisons. Odds ratios (OR) were reported with the corresponding 95% confidence interval (CI) to assess the strength of association between CM cases and MRI markers compared to matched comparisons.

Results

From the PBTSG database of 108 posterior fossa cases, 11 children who presented with CM after the resection of their tumor were identified (prevalence of CM among PF tumors = 10%). Eleven CM patients were matched with 11 comparisons from the PBTSG database, who also underwent PF surgery but did not acquire CM (Table 1). The mean age distribution of the CM cases was 7.43 years (SD 2.4), while the mean age of the matched comparisons was 7.03 years (SD 3.8). The tumor pathology in 10 of 11 CM patients was medulloblastoma, and the remaining one patient had a pilocytic astrocytoma; these tumor types were matched accordingly in the comparison group. Although patients were not matched based on sex, 3 of the 11 CM cases were female while 4 of the 11 comparison patients were female.

Surgical and MRI factors

Based on pre-operative MRI scanning, the mean tumor size in the CM group was 3.73 cm compared to 4.64 cm in the comparison group. Table 2 depicts the number of cases and comparisons that were positive for each variable. Certain study participants were omitted from analysis of calcification and infarct variables due to an absence of gradient imaging or diffusion-weighted imaging. While the results did not reach statistical significance, Table 2 demonstrates the strength of association between MRI characteristics and CM (OR and 95% CI) for each variable. Of the listed factors, tumor attachment to the floor of the fourth ventricle (OR 6; 95% CI 0.7–276), calcification or hemosiderin deposits (OR 7; 95% CI 0.9–315.5), necrosis (OR 3; 95% CI 0.2–157.5), moderate/high hydrocephalus (OR 3; 95% CI 0.2–157.5), post-operative infarcts and bleeds (OR 5; 95% CI 0.5–236.5) and gross total surgical resection (OR 3; 95% CI 0.5–30.4) had positive association with CM. Tumor attached to floor of 4th ventricle (Fig. 1 A—a, b), calcification/hemosiderin deposits (Fig. 1 B—a, b), necrosis, moderate to severe hydrocephalus, gross total resection and post-operative infarcts (Fig. 1 C—a–d) had a higher incidence in the CM group. To validate anecdotal expert opinion of the intraoperative events thought to be associated with CM, we have included qualitative evidence, which have captured these events to occur more frequently in the CM group than the comparison group (please refer to Table 3). Vasogenic edema (OR 0.4; 95% CI 0.04–2.4), leptomeningeal enhancement (OR 0.3; 95% CI 0.01–4.1) and metastasis in head or spine (OR 0.6; 95% CI 0.05–5.8) were more prevalent in the comparison group.

Table 1 Demographic data for cases and comparisons: cases were matched based upon age and tumor type with other brain tumor patients in our database

Patient characteristics	CM cases (n = 11)	Comparisons (n = 11)
Age at initial diagnosis		
Mean (SD)	7.43 (2.4)	7.03 (3.8)
Sex		
Male/female	8/3	7/4
Tumor type		
Medulloblastoma	10	10
Pilocytic Astrocytoma	1	1

Discussion

CM is a condition which occurs post-operatively, following the removal of a PF tumor in children. This condition may have an iatrogenic cause, as the disruption of the dentato-thalamo-cortical (DTC) pathway during surgery has been hypothesized as a potential trigger [1, 5]. Avula et al. reported a significant association between CM and diffusion abnormalities in the dentate nucleus, superior cerebellar peduncle, and mesencephalic tegmentum immediately post-operatively [8]. A recent case-control study employing diffusion tensor imaging noted that CM patients showed white matter changes in the superior cerebellar peduncle; these changes remained evident months following the surgery [9]. Perreault et al. evaluated time-dependent changes to the DTC pathway following posterior fossa tumor resection in children and found that post-operatively, the dentate nuclei underwent progressive atrophy and the DTC pathway showed continuous structural changes [10]. While certain diffusion tensor scans of CM patients have shown DTC disruption, some of these scans took place before, or years after surgery and thus cannot be associated with CM [5]. There was no temporal association between MRI scans showing DTC disruption and the patient's CM symptoms. We aimed to determine whether there are any surgical or MRI factors associated with CM in order to improve the understanding of CM's pathophysiology. Post-operative infarcts, calcification, and disruption of the floor of the fourth ventricle may be implicated in the development of CM rather than attributing this to DTC pathway disruption alone. If the presence of calcification is indeed associated

Table 2 MRI characteristic results: the table depicts the number of cases and comparisons that were deemed positive for each variable and the odds ratios and confidence intervals for each variable

Variables	Odds ratio (CI 95%)	Cases	Comparisons
Attached to floor of 4th ventricle	6.0 (0.7, 276.0)	10 (91%)	5 (45%)
Head or spine metastasis	0.6 (0.05, 5.8)	3 (27%)	4 (36%)
Leptomeningial enhancement	0.3 (0.01, 4.1)	2 (18%)	4 (36%)
Calcification or hemosiderin deposits	7.0 (0.9, 315.5)	7 (70%)	2 (18%)
Necrosis	3.0 (0.2, 157.5)	6 (55%)	4 (36%)
Vasogenic edema	0.4 (0.04, 2.4)	2 (18%)	5 (45%)
Moderate/high hydrocephalus	3.0 (0.2, 157.5)	10 (91%)	8 (73%)
Post-operative infarcts	5.0 (0.5, 236.5)	8 (73%)	4 (44%)
Gross total resection (Surgical)	3.0 (0.5, 30.4)	8 (73%)	4 (36%)

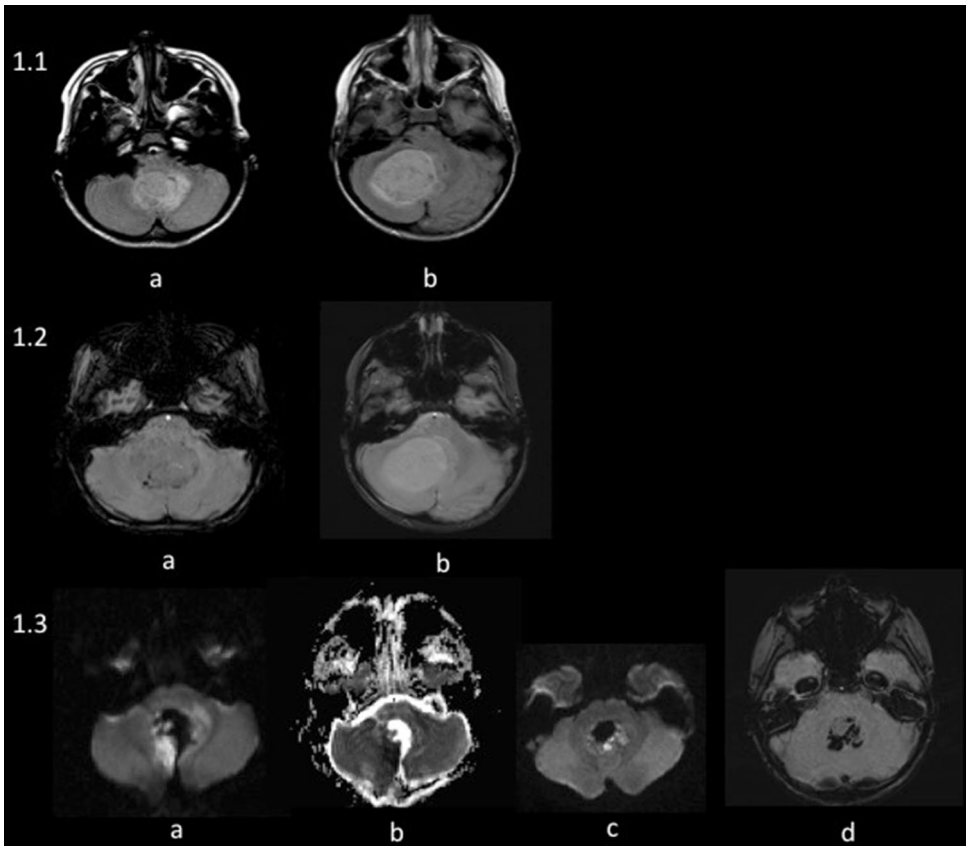


Fig. 1 **A** Pre-operative fourth ventricle floor attachment. Axial flair imaging was used to determine whether tumor was arising from the floor of the fourth ventricle. Figure 1 **A** (*a*) depicts an example of tumor attached and centered in the floor of the fourth ventricle in a CM case, which was present in 10 of 11 CM cases, and present in 5 of 11 non-cases. Figure 1 **A** (*b*) is an example of tumor not attached to the floor of the fourth ventricle in a control case, as the lesion is arising within the parenchyma of the *right* cerebellar hemisphere in the dentate nucleus area. **B** Pre-operative calcification and hemosiderin deposits. Susceptibility weighted imaging was used to determine if there was calcification in the tumor. Figure 1 **B** (*a*) depicts multiple foci of abnormal magnetic susceptibility within the tumor in a CM case, representing either micro-calcifications or hemosiderin deposits. This was present in 7 of 10 CM patients, and 2 of 11 non-cases. Figure 1 **B** (*b*) is an example of a tumor without evidence of areas with abnormal magnetic susceptibility in a control case. **C** Post-operative infarcts/contusions. Diffusion weighted imaging was used to determine whether the cases and comparisons showed infarcts post-operatively. Figure 1 **C** (*a*) is an example of a b1000 image used alongside a Fig. 1C (*b*) ADC map to determine a post-operative infarct/contusion. Figure 1 **C** (*c*) is a b1000 image used in conjunction with a susceptibility weighted image (Fig. 1 **C** (*d*)) to determine that there was no visible evidence of infarct but only blood products adjacent to the surgical bed walls. 8 of 11 CM cases had DWI infarcts in their immediate post-operative scan in comparison to 4 of 9 non-cases

with cerebellar mutism, this could serve to warn surgeons that there may be an increased likelihood of CM.

The majority (75–90%) of medulloblastomas arise from the roof of the fourth ventricle [11]. The higher prevalence of floor of the fourth ventricle attachment in CM patients may suggest that the disruption of the floor of the fourth ventricle during surgery may result in CM. A recent study examining the molecular subtypes of medulloblastoma found that the sonic hedgehog tumor group had a lower incidence of CM in comparison to wingless, Group 3, and Group 4 [12]. The sonic hedgehog subgroup does not tend to arise from the floor of the fourth ventricle, a trait more predominant in Groups 3 and 4 [13]. This supports the hypothesis that tumor attachment to the floor of the fourth ventricle is implicated in the development of cerebellar mutism. If disruption of this region is significantly associated with CM, then surgeons could take a less invasive approach while removing tumor from the floor of the ventricle, favoring a near-total resection over a GTR [14]. In addition, there could be an attempt to use the pre-operative imaging to predict outcome if the tumor is involving the floor of the fourth ventricle. Thompson et al. suggest that the influence of GTR on medulloblastoma survival rates is not as significant as previously suggested [14]. Interestingly, the large majority of the CM patients in our study were diagnosed with medulloblastoma [1, 3]. Outcomes and goals of gross-total resection and risk of CM should be considered when tumors such as medulloblastoma involve

Table 3 Association between imaging and intraoperative events and development of cerebellar mutism

Patient ID	Year of surgery	Intraoperative findings	Pre-operative MRI attachment to fourth ventricle?	Intraoperative observation of attachment to fourth ventricle	Residual left behind?	Intraoperative disruption in vital signs
Cerebellar mutism group						
1	2009	Initially there was great deal of venous bleeding controlled with bipolar cautery. On the left, the tumour extended laterally into the cerebellar hemisphere. Floor of the fourth exposed and lined with patties under microscopy. Debulked tumour on the floor of the fourth with suction and piecemeal dissection with tumour forceps. The surgeons worked from the aqueduct inferiorly towards the craniocervical junction with a 1 mm carpet and approximately 3 × 3 mm patch was left on the floor of the 4th bilaterally. PICA on the right was surrounded by tumour. Clinically deteriorated 48 h post-op (resection and VP shunt insertion) with nystagmus, bradycardia, quadriparesis and respiratory distress—urgent OR for posterior fossa decompression for brainstem compression—motor recovery but cerebellar mutism syndrome with severe irritability—commenced on chemotherapy thereafter but soon after developed motor weakness with MRI demonstrating spinal met with cord compression—palliated—RIP May 2009 (3 months post-diagnosis).	Left lateral wall	Floor	Yes	None intraoperatively but post-operative course—deterioration and brainstem compression did occur in PICU
2	2004	The floor of the 4th was very rapidly visualized and protected with cottonoids. The tumour appeared to be predominantly fixed to the roof of the fourth ventricle on the left side. Most of the tumour was very easily suckable, and removable with biopsy forceps as well as the Cavitron ultrasonic aspiratory. Towards the left side, however, the tumour in one portion was significantly firmer, and had to be sharply mobilized, also using bipolar cautery, to allow its excision. There was a brisk bleeder at one point just above the roof of the aqueduct, and coagulation was used moderate amounts to control this. One other pesky bleeder occurred just in the region of the 7th nucleus in the floor of the fourth on the left. This was coagulated superficially and hemorrhage controlled with patties.	Left lateral wall/floor	Roof	No	No

Table 3 (continued)

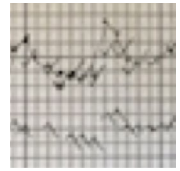
Patient ID	Year of surgery	Intraoperative findings	Pre-operative MRI attachment to fourth ventricle?	Intraoperative observation of attachment to fourth ventricle	Residual left behind?	Intraoperative disruption in vital signs
3	2003	The tumour was adherent to the floor of the 4th ventricle along the left side below the region of the facial colliculus and this was gradually dissected free using bipolar cautery and gentle elevation. As the tumour was being elevated, there was some transient bradycardia, which picked up immediately after release of tension. Soon thereafter, the patient became tachycardic and remained intermittently so throughout the procedure. At times, anesthesia reported the patient was also hypertensive, without this being directly related in any way, which we could identify to our surgical manipulation. The Cavitron ultrasonic aspirator was used to remove the bulk of the tumour. It seemed to take its origin from the vermis and roof to the fourth ventricle. At the completion of excision, the surgeons inspected the removal cavity and there was no evidence of tumour remnant. At the completion of the surgery, anesthesia noted the child was hyperventilating with tidal volumes approximately 2x of that predicted by his weight. He as also hypertensive despite narcotics, beta and alpha blockers. He was taken immediately to CT post-op to rule out bleed. None seen.	Right posterolateral wall	Floor	No	Transient bradycardia followed by persistent tachycardia and hypertension 
4	2004	The vemis was gently elevated and some gelatinous appearing grey tumour was visualised. Unable to sufficiently elevate the vermis to do the excision, the inferior 1/4 of the vermis in the midline was opened using bipolar cautery and suction. Unfortunately we did notice that it appeared to be infiltrating the floor of the 4th ventricle bilaterally. We thinned it down here, but elected not to follow inwards into the floor.	Right posterolateral wall	Floor	Yes	No

Table 3 (continued)

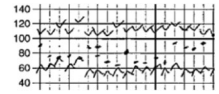
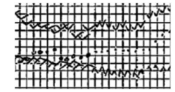
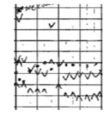
Patient ID	Year of surgery	Intraoperative findings	Pre-operative MRI attachment to fourth ventricle?	Intraoperative observation of attachment to fourth ventricle	Residual left behind?	Intraoperative disruption in vital signs
5	2012	With the use of the microscope, careful dissection was made through the anterior cerebellar fissure and the tumour was accessed through the left side of the vermis. The 4th ventricle was opened and the tumour was immediately encountered. Patties and cottonoids were used to protect the floor of the 4th. Tumour resected in piecemeal fashion with Roton instruments. Gross total resection was achieved.	Inferolateral wall	–	No	Yes 
6	2005	The tumour was initially debulked in the midline all the way to the top and then turned our attention to the lateral aspects of this tumour. Using the Roton micro instruments, a plane was developed and the Cavitron used to resect the tumour. The tumour was moderately vascular. The PICA on the right was preserved. The tumour was attached to the floor of the 4th. We were able to shave off the tumour with the CUSA. Felt gross total resection was achieved.	–	Floor	Yes	1 episode of hypotension 
7	2012	The tumour was very adherent to the surrounding cerebellar tissue. Well delineated from the floor of the 4th however as it came out of the cerebellar tissue, it was very vascular and adherent. In the process of dissection, when there was some blood into the floor of the 4th, a rise in blood pressure was noted. No signs of raised ICP so it was determined that it was secondary to blood irritation. Piecemeal removal of the tumour with cauterization along the tumour surface while debulking. Occasionally, there was some tumour-brain interface, especially at the floor of the 4th. The surgeons did not feel the tumour was invading the floor of the 4th but was invading the cerebellar tissue. Gross total resection was achieved.	Right inferolateral wall	–	No	1× unexplained rise in BP 180/110 ?due to retraction on brainstem 

Table 3 (continued)

Patient ID	Year of surgery	Intraoperative findings	Pre-operative MRI attachment to fourth ventricle?	Intraoperative observation of attachment to fourth ventricle	Residual left behind?	Intraoperative disruption in vital signs
8	2003	Once the bulk of the tumour was removed, the floor of the 4th was visualised. The tumour was carpeting the inferior third of the floor of the 4th and this area was highly vascular. Felt not wise to attempt to resect this portion and left a residual behind. At the upper pole, the tumour plugging the aqueduct was easily removed and the tumour appeared to be infiltrating into the roof of the aqueduct. *Tumour boards note states*—Surgeon commented on 1.4 cm tumour unable to resect safely on the floor of the 4th. Did well but 36 h post-operatively developed posterior fossa syndrome with cerebellar mutism. A subsequent CT showed edema with attenuation of the right posterior medial pole of the right cerebellum - ?secondary to thrombus of the superior cerebellar artery - MRI suggested hemorrhagic infarct which surgeon felt unlikely.	Left lateral wall	Floor	Yes	No
9	2009	After central debulking, the apparent capsule of the tumour was lifted and a plane between the tumour and the floor of the 4th was visualized. A patty was placed to protect the floor and the tumour was lifted from the inferior pole upwards using biopsy forceps to hold the capsule of the tumour. The right lateral aspect extended into the cerebellar hemisphere where a good plane was found. The superior part of the tumour was pulled out of the cerebral aqueduct. Questionable 1 mm plaque of tumour on the right lateral floor of the 4th was coagulated using bipolar electrocautery and hemostasis achieved. Surgical gross total resection was achieved.	Left inferolateral wall	Floor	No	No

Table 3 (continued)

Patient ID	Year of surgery	Intraoperative findings	Pre-operative MRI attachment to fourth ventricle?	Intraoperative observation of attachment to fourth ventricle	Residual left behind?	Intraoperative disruption in vital signs
10	2014	The floor of the 4th was protected with a neuropattie. The ultrasonic aspirator was used to resect the tumour in a methodical fashion proceeding inferiorly up until the aqueduct of Sylvius was reached. At the level of the pons in the inferior part of the 4th ventricle, the tumour was attached to the brain stem and this part of the tumour could not be safely resected. The thickness of the tumour left behind was approximately 2–3 mm. At the right CP angle, tumour was also left behind because of the depth of dissection and vascularity. There was bleeding from the region of the brain stem to the floor of the 4th ventricle and this bleeding was controlled with irrigation and Surgicel.	Uncertain	Floor	Yes	No
11	2013	The tumour was mainly intraventricular and some sporadic adherence just on the side of the floor of the 4th ventricle. Definite involvement of the foramina of Luschka on the left side with 2 major vascular feeders seen. After the dural opening under microscope visualization, the 4th ventricle was visualized and the tumour was identified. Attempt to spare the en passage vessel was successful however the rest of the feeding arteries were cauterized and cut. A pattie was placed on the floor of the 4th to protect it while removing the tumour. Gross total resection was achieved.	Floor	Floor	No	No
Control group						
1	2009	EVD sited first. Frozen section: L'hermitte-Duclos syndrome or dysplastic gangliocytoma of the cerebellum, well differentiated MB or polymicrogyria. Because several differential diagnoses were benign and could be addressed at a more elective time in the future, the surgeons decided to stop 1 cm short of the mid-brain to avoid damage to neural tissue.	–	Floor	Yes	No

Table 3 (continued)

Patient ID	Year of surgery	Intraoperative findings	Pre-operative MRI attachment to fourth ventricle?	Intraoperative observation of attachment to fourth ventricle	Residual left behind?	Intraoperative disruption in vital signs
2	2010	During our procedure, going deeply and aiming anteriorly, we had exposed the roof of the 4th ventricle. When we reached superiorly, we noticed that the anterior part of the tumour was attached to the brain stem. Tumour on the floor of the 4th was left behind to reduce the morbidity for the patient.	Left lateral wall	Floor	Yes	No
3	2008	The medullary striaie were visualized which gave a landmark of the surgeon's progression up to the superior aspect of the 4th. The aqueduct was finally visualized and a large amount of the tumour was found clogging this area. The surgeons removed all of the tumour around the aqueduct until very good flow of CSF could be visualized through the clear aqueduct. Gross total resection achieved.	–	–	No	No
4	2012	Once we were satisfied with the tumour removal anteriorly, we turned our attention to the roof of the fourth ventricle were there was some residual tumour adherent. Bipolar cautery and suction was used to resect the balance of the tumour in this area. We were careful not to injure the cerebellar vermis. Gross total resection achieved.	–	Roof	No	No
5	2011	The durotomy was performed and the tumour cyst was apparent. The surgeons dissected around the cyst. As the cyst was mobilized, a draining vein to the transverse sinus was torn and bleeding from the right transverse sinus ensued. 1 PRC administered. The anterior cyst wall was pressing against the brainstem. The surgeon stopped at this point not wanting to dissect the cyst off of the brainstem and instead chose to coagulate the cyst and leave the remaining anterior wall against the brain stem.	Uncertain	Floor	Yes	No

Table 3 (continued)

Patient ID	Year of surgery	Intraoperative findings	Pre-operative MRI attachment to fourth ventricle?	Intraoperative observation of attachment to fourth ventricle	Residual left behind?	Intraoperative disruption in vital signs
6	2009	The tumour was ultimately debulked and dissected until a depth of approximately 3 cm was reached and the floor of the tumour bed was found to reveal only gliotic white matter. The surgeons then placed retractors gently in the fourth ventricle to visualize the shiny white floor. The surgeons explored the foramen of Magendie and the right foramen of Luschka and did not see any subsequent tumour.	–	–	No	No
7	2010	One could see multiple small areas of tumour in the subarachnoid space overlying the cerebellum indicating extensive leptomeningeal spread. After separating the tonsils, one could see a pale looking tumour that was firmly attached and embedding the right PICA. Tumour was left surrounding vessel to avoid vascular injury. The floor and aqueduct was protected throughout the debulking. The tumour blended into the brain tissue and there was no plane between the tumour and the brain. The tumour blended in with the fourth ventricle laterally and we intentionally left some tumour behind in order to avoid any injury to the floor of the fourth ventricle.	Roof	Floor	Yes	No
8	2014	On opening the dura, a portion of the tumour came out spontaneously. The tumour is highly vascular. There was no obvious capsule. The attachment seems to be probably at the superior or inferior medullary vellum and we did not see any obvious invasion of the floor of the fourth ventricle.	Left medial/ superolateral wall	Roof	No	No

Table 3 (continued)

Patient ID	Year of surgery	Intraoperative findings	Pre-operative MRI attachment to fourth ventricle?	Intraoperative observation of attachment to fourth ventricle	Residual left behind?	Intraoperative disruption in vital signs
9	2008	It became obvious that the tumour was completely stuck to the floor of the fourth ventricle on the right side. We were then forced to leave a carpet of tumour on the right side and on the fourth ventricle. Given the fact that this patient has multiple other tumours with respect to the spinal canal, it was not felt that it was worth pursuing a very aggressive resection with possible significant morbidity and it was decided as this point to stop. We had decompressed the fourth ventricle nicely, and there was good flow of CSF from the aqueduct.	Uncertain	Floor	Yes	No
10	2010	We placed patties on the floor of the fourth and visualized the tumour itself was able to be gently manipulated and lifted off the floor of the fourth ventricle was no apparent adherence. The tumour appeared to rise from the superior vermis and the superior medullary velum/roof of the fourth. The entire floor and lateral aspects of the fourth ventricle were visualized and found to be free of tumour and CSF flow excellent. Gross total resection achieved.	Posteroinferior wall	Roof	No	No
11	2008	The surgeons noticed the aggressive CSF indicating that the superior medullary velum to which the tumour was adherent had been encountered. The tumour was dissected using gentle traction using the Russian forceps and a pattie placed on the floor of the fourth to protect it from injury. A very large tumour was resected in total and measured more than 5 cm in length. Gross total resection achieved.	–	Roof	No	No

the floor of fourth ventricle [14]. CM's association with the floor of the fourth ventricle may alter a surgeon's approach but further research is required in order to determine the exact cerebellar tract affected, which could detail preventative measures. For every neurosurgeon operating in the proximity of the floor of the fourth ventricle, the result of each surgical movement dynamically changes the next. This pilot study supports our senior surgeon's intraoperative anecdotal experience that disruption of the floor of the fourth ventricle is associated with post-operative MRI changes in our CM group. Our study serves as a caution for neurosurgeons. If disruption of the floor of the fourth ventricle is associated with CM, surgeons should exercise extreme caution until they have delineated the attachment of the tumour as we have observed a notable discrepancy between pre-operative MRI reports and intraoperative finding of tumour attachment.

Higher grade tumors such as medulloblastoma can be more difficult to resect completely relative to most pilocytic astrocytomas, as pilocytic astrocytomas are often well-delineated [15]. Medulloblastoma tumors can be infiltrative, requiring more dissection of the brain-tumor interface, which may account for the CM occurring post-operatively. The presence of areas with restricted diffusion surrounding the surgical bed post-operatively was higher in the CM group. This may represent areas of contusion or ischemia of the parenchyma, which is likely caused during surgery, and a lack of blood supply in these regions may be the underlying cause CM. The infarcts or contusions were located around the floor of the fourth ventricle, suggesting a relationship between these two variables. Therefore, disruption of the floor of the fourth ventricle may subsequently result in ischemia and thereby may predicate the development of CM.

The variables associated with a lack of CM (vasogenic edema, leptomeningeal enhancement, and metastasis in the head or spine) are factors that may cause a surgeon to avoid a GTR. Therefore, vasogenic edema, leptomeningeal enhancement, and metastasis may be related to the subtotal resection variable, all of which are correlated with a lack of CM.

Strengths and limitations

There are certain limitations to the design of this study, inherent to observational retrospective designs. This study was underpowered to draw a strong conclusion; 95% confidence intervals lacked precision due to the relatively small sample size. Certain patients did not have gradient imaging or diffusion-weighted imaging sequences on their immediate pre-operative and post-operative scans. This resulted in fewer cases and comparisons to be reviewed in the current study. MRI imaging within 48 h pre-operatively and post-operatively were reviewed, but post-operative time of MRI varied between the patients in the study.

The comparative nature of the study is a strength, as the case-comparison model allows for an examination of factors associated with CM. The data registry is another strength of the study as it contains patient data compiled from clinical, surgical and MRI charts and represents the total pediatric brain tumor population at McMaster from 2002 to 2015. Additionally, 5% of this database was double-checked for accuracy. The blinded neuro-radiologist examination is another strength of the current study, as MRI evaluation was not influenced by the knowledge of whether a patient had CM or not. The reports of this neuro-radiologist were also double-checked with the previous MRI reports for data accuracy.

Conclusion

Our study explores some of the putative factors leading to CM development. We found that post-operative peri-ventricular infarcts/bleeds, tumor attached to the floor of the fourth ventricle, and calcification were more prevalent in CM cases than in controls. It would be beneficial to undertake a prospective multi-center study in order to adequately address the question. Insights from these findings guides further investigation of the determinants and management of CM in order to potentially minimize its development and predict onset.

Funding No funding to disclose.

Compliance with ethical standards

Conflict of interest All the authors declares that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Reed-Berendt R, Phillips B, Picton S, Chumas P, Warren D, Livingston JH, Hughes E, Morrall M (2014) Cause and outcome of cerebellar mutism: evidence from a systematic review. Childs Nerv Syst 30:375–385. doi:10.1007/s00381-014-2356-0
2. Di Rocco C, Chieffo D, Frassanito P, Caldarelli M, Massimi L, Tamburrini G (2011) Heralding cerebellar mutism: evidence for pre-surgical language impairment as primary risk factor in posterior fossa surgery. Cerebellum 10:551–562. doi:10.1007/s12311-011-0273-2

3. Law N, Greenberg M, Bouffet E, Taylor MD, Laughlin S, Strother D, Fryer C, McConnell D, Hukin J, Kaise C, Wang F, Mabbott DJ (2012) Clinical and neuroanatomical predictors of cerebellar mutism syndrome. Neuro-Oncology 14:1294–1303. doi:10.1093/neuonc/nos160
4. Patay Z (2015) Postoperative posterior fossa syndrome: unraveling the etiology and underlying pathophysiology by using magnetic resonance imaging. Childs Nerv Syst 31(10):1853–1858. doi:10.1007/s00381-015-2796-1
5. Van Baarsen KM, Grotenhuis JA (2014) The anatomical substrate of cerebellar mutism. Med Hypotheses 82:774–780. doi:10.1016/j.mehy.2014.03.023
6. Pitsika M, Tsitouras V (2013) Cerebellar mutism. J Neuros-Pediatr 12:604–614. doi:10.3171/2013.8.peds13168
7. Gajjar A, Sanford RA, Bhargava R et al (1996) Medulloblastoma with brain stem involvement: the impact of gross total resection on outcome. Pediatr Neurosurg 25(4):182–187. doi:10.1159/000121121
8. Avula S, Kumar R, Pizer B, Pettorini B, Abernethy L, Garlick D, Mallucci C (2015) Diffusion abnormalities on intraoperative magnetic resonance imaging as an early predictor for the risk of posterior fossa syndrome. Neuro-oncology 17(4):614–622. doi:10.1063/neuonc/nou299
9. McEvoy, S et al (2016) Longitudinal cerebellar diffusion tensor imaging changes in posterior fossa syndrome. Neuroimage Clin 12:582–590. doi:10.1016/j.nicl.2016.09.007
10. Perreault S, Lober RM, Cheshier S, Partap S, Edwards MS, Yeom KW (2014) Time-dependent structural changes of the dentatothalamic pathway in children treated for posterior fossa tumor. Am J Neuroradiol 35:803–807. doi:10.3174/ajnr.a3735
11. Plaza M, Borja M, Altman N, Saigal G (2013) Conventional and advanced MRI features of pediatric intracranial tumors: posterior fossa and suprasellar tumors. Am J Roentgenol 200(5):1115–1124. doi:10.2214/AJR.12.9725
12. Moxon-Emre et al (2016) Intellectual outcome in molecular subgroups of medulloblastoma. J Clin Oncol 34:4161–4170. doi:10.1200/JCO.2016.66.9077
13. Perreault S et al (2014) MRI surrogates for molecular subgroups of medulloblastoma. Am J Neuroradiol 35(7):1263–1269. doi:10.3174/ajnr.A3990
14. Thompson E, Hielscher T, Bouffet E et al (2016) Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup. Lancet Oncol 17:484–495. doi:10.1016/s1470-2045(15)00581-1
15. Pollack I (2011) Multidisciplinary management of childhood brain tumors: a review of outcomes, recent advances, and challenges. J Neurosurg Pediatr 8:135–148. doi:10.3171/2011.5.PEDS1178