Molecular correlates of cerebellar mutism syndrome in medulloblastoma

Rashad Jabarkheel, BS[1*], Nisreen Amayiri, MD[2,3*], Derek Yecies, MD[1], Yuhao Huang, BS[1], Sebastian Toescu, MB.ChB[4], Liana Nobre MD[3], Donald J. Mabbott, PhD[3,5,6], Sniya V. Sudhakar, DNB[7], Prateek Malik, MD[7], Suzanne Laughlin, MD[8], Geeta Chacko, MBBS, PhD[9], Leni G. Mathew, MD[10], Paul G. Fisher, MD[11], Darren Hargrave MBBS[4], Ute Bartels[3], Uri Tabori MD[3], Stefan M. Pfister MD[12], Kristian Aquilina, MD[13], Michael D. Taylor, MD, PhD[14,15,16], Gerald A. Grant, MD[1], Eric Bouffet MD[3], Kshitij Mankad, MBBS[17], Kristen W. Yeom, MD#, Vijay Ramaswamy, MD, PhD[3,14,15]#.

1) Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA (RJ, DY, YH, GAG)

2) Department of Oncology, King Hussein Cancer Center, Amman Jordan (NA)

3) Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON (NA, DJM, LN, EB, VR)

4) University College London, Great Ormond Street Institute of Child Health, London, UK

5) Department of Psychology, University of Toronto, Toronto, ON (DJM)

6) Programme in Neuroscience and Mental Health, Hospital for Sick Children, Toronto, ON (DJM)

7) Department of Radiology, Christian Medical College, Vellore, Tamil Nadu, India. (SVS, PM)

8) Division of Neuroradiology, Hospital for Sick Children, Toronto, ON (SL)

9)Department of Pathology, Christian Medical College, Vellore, Tamil Nadu, India. (GC)

10) Department of Pediatrics, Christian Medical College, Vellore, Tamil Nadu, India. (LGM)

11) Department of Neurology & Division of Child Neurology, Stanford University, Palo Alto, CA, USA. (PGF)

12) Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ), and German Cancer Consortium (DKTK), Heidelberg, Germany (SMP)

13) Neurosurgery Department, Great Ormond Street Hospital for Children, London, UK (KA)

14) Division of Neurosurgery, Hospital for Sick Children, Toronto, ON (MDT)

15) Department of Medical Biophysics, University of Toronto, Toronto, ON (MDT, VR)

16) Programme in Developmental and Stem Cell Biology, Hospital for Sick Children, Toronto, ON (MDT, VR)

17) Department of Radiology, Great Ormond Street Hospital for Children, London, UK (KM)

18) Department of Radiology, Stanford University School of Medicine, Stanford, CA, USA (KY)

Corresponding Author:

Vijay Ramaswamy

555 University Ave

Hospital for Sick Children

Toronto, ON, M5G 1X8

Phone: 4168137654 Fax: 4168135327

vijay.ramaswamy@sickkids.ca

or

Kristen Yeom

725 Welch Rd., MC 5654

Lucile Packard Children's Hospital

Palo Alto, CA, 94304

Phone: 650-721-2388 Fax: 650-723-1909

kyeom@stanford.edu

Running Title: Cerebellar mutism and medulloblastoma subgroup

* co-first authors

co-senior authors

Funding: VR is supported by operating funds from the Canadian Institutes of Health Research, American Brain Tumor Association, the Garron Family Cancer Center, Meagan's Walk, b.r.a.i.n.child, Nelina's Hope, the C.R. Younger Foundation and the Brain Tumour Foundation of Canada. NA was supported by an ASCO Life Fellowship from the Conquer Cancer Foundation. KY was supported by Lucile Packard Children's Foundation Brain & Behavior Center Award in Pediatric Neurosciences

Conflict of Interest: The authors declare no conflict of interest.

Authorship: NEW: Conceptualization, NA, KY, VR.; Methodology, RJ, NA, KM, KWY, VR; Investigation, RJ, NA, DY; Data Curation, RJ, NA, DY, LN, SVS, PM, GC, LGM.; Formal Analysis: RJ, KWY, VR; Writing – Review & Editing, RJ, KWY, VR; Resources, YH, ST, SVS, PM, SL, GC, LGM, PGF, DH, EB, UB, UT, MDT, SMP, KA, GAG, KM, KWY, VR, Project Administration, KWY and VR; Supervision, KWY, VR.; Funding Acquisition, KWY, VR.

Manuscript word count: Abstract - 243, Text - 1871, References - 676

Abstract:

Introduction: Cerebellar Mutism Syndrome (CMS) is a common complication following resection of posterior fossa tumors, most commonly after surgery for medulloblastoma. Medulloblastoma subgroups have historically been treated as a single entity when assessing CMS risk, however, recent studies highlighting their clinical heterogeneity suggest the need for subgroup-specific analysis. Here, we examine a large international multicenter cohort of molecularly characterized medulloblastoma patients to assess predictors of CMS.

Methods: We assembled a cohort of 270 molecularly characterized medulloblastoma subjects with available neuroimaging from four sites globally including Great Ormond Street Hospital, Christian Medical College and Hospital, Hospital for Sick Children, and Lucile Packard Children's Hospital. Age at diagnosis, gender, tumor volume, and CMS development were assessed in addition to molecular subgroup.

Results: Overall, 25.9% of patients developed CMS. CMS patients were younger (mean difference -2.73 years ± 0.8, P=0.0027) and had larger tumors (mean difference 16.99 cm^3 ± 5.287, P<0.0001) that were more midline (OR=20.03, P<0.0001). On multivariable analysis adjusting for age, sex, midline location, and tumor volume, WNT (adjusted OR=5.06, P=0.027) and Group 4 (adjusted OR=7.42, P=0.004) tumors were found to be independently associated with higher risk of CMS as compared to SHH tumors.

Conclusions: Herein we show in a large cohort of molecularly characterized medulloblastoma that subgroup is a very strong predictor of CMS development, owing primarily to larger midline tumours presenting in WNT and Group 4 patients. These findings have significant implications for future studies of prevention and early treatment of CMS.

Keywords: Posterior Fossa Syndrome, Cerebellar Mutism, Medulloblastoma, Postoperative Cerebellar Mutism, Cerebellar Affective Disorder

Key Points:

- Molecular subgroup is a powerful predictor of developing cerebellar mutism syndrome after resection for medulloblastoma
- Tumor volume in WNT and Group 4 tumours is highly predictive of developing cerebellar mutism syndrome consistent with large midline tumors with long pre-diagnostic intervals predisposed to its development.

Importance of the Study

Medulloblastoma is now clearly recognized as being four distinct molecular subgroups with clear clinical differences. Cerebellar mutism syndrome is a common occurrence after surgery for medulloblastoma, however accurate risk prediction remains a challenge. We show that by incorporating molecular subgroup into risk modeling, we can more accurately predict the occurrence of cerebellar mutism. The observation that larger WNT and Group 4 medulloblastoma further support the hypothesis that debulking of midline large tumours more frequently perturbs proximal cerebellar output tracts. Our study provides further evidence of the clear clinical differences between the four medulloblastoma subgroups, and provides a potential framework for pre-operative prediction of the development of cerebellar mutism. Applying radiogenomic pre-operative prediction of subgroup can potential allow the introduction of new preventative efforts for medulloblastoma patients at highest risk for the development of cerebellar mutism.

Introduction

Cerebellar mutism syndrome (CMS), also known as posterior fossa syndrome, is a common condition which develops after surgery for cerebellar tumours in children.[1-3] CMS is a complex constellation of neurological symptoms but there is a consensus that post-operative pediatric CMS is characterized by delayed onset mutism/reduced speech and emotional lability.[1] Other symptoms can co-occur including hypotonia, oropharyngeal dysfunction/dysphagia and brainstem dysfunction. The mutism is transient but speech and language dysfunction often persist with frequent long-term neurocognitive impairment.[4-6] The most common setting it is observed in is after resections for medulloblastoma, and in several series evaluating predictors of long-term neurocognitive sequelae, CMS is a significant predictor of reduced IQ. The etiology of CMS is likely secondary to disruption of cerebellar outflow tracts, and previously it has been suggested that the splay of the superior cerebellar peduncle pre-surgically has a role in the pathogenesis of CMS.[7,8] Other studies of clinical and neuroanatomical predictors have suggested larger tumour size, left handedness and white matter changes in the cerebello-thalamo-cortical pathways as significant predictors of CMS.[4] Surgical factors have been shown across several studies to not modify the risk of CMS suggesting that new approaches are needed to potentially identify patients at risk.[8]

Over the past decade advances in genomics have revealed significant heterogeneity across medulloblastoma, where it is now clear that medulloblastoma comprises at least four distinct molecular subgroups with highly disparate demographics, genetics, cell of

origin and outcomes.[9-13] Indeed, the four subgroups, termed WNT, SHH, Group 3 and Group 4 represent distinct disease entities, and can even be distinguished reliably using conventional MRI, based partly on their distinct locations.[14-18] SHH tumours are almost always within the cerebellum, and frequently located laterally in the cerebellar hemispheres, WNT tumours frequently arise out of the lateral recess, and Group 3 and 4 occupy the 4th ventricle.[13,14,19,20] Previously it has been shown that Group 4 have worse neurocognitive outcomes, and it has been suggested that CMS is less common in SHH patients.[6] However, no comprehensive study has been conducted to evaluate whether subgroup can be used as a predictor of CMS. In order to evaluate the correlation between medulloblastoma subgroup and the development of CMS, we assembled a large cohort of 270 patients, and show a clear subgroup specificity of CMS, with larger Group 4 tumours having a clear preponderance to the development of CMS.

Materials and Methods

Study Cohort: This international multicenter study was approved by the Institutional Review Board or research ethics board of all participating institutions including: Christian Medical College and Hospital (CMCH; Vellore, Tamil Nadu, India), Great Ormond Street Hospital (GOSH; London, England, United Kingdom), Hospital for Sick Children (HSC; Toronto, Ontario, Canada), and the Lucile Packard Children's Hospital (LPCH; Stanford, California, United States). All medulloblastoma patients at each institution were reviewed from 2000-2018. Patients were screened for inclusion based on the availability of pre-operative magnetic resonance imaging (MRI) allowing for measurement of tumor volume, molecular subgrouping, and the availability of perioperative clinical notes allowing for

determination of CMS development. Patient age at diagnosis and gender were additionally gathered on review of patient charts. In total, we assembled a cohort of 270 medulloblastoma patients from our four sites as follows: CMCH (n=87), GOSH (n=25), HSC (n=111), and LPCH (n=47). A summary of patient demographics and clinical characteristics by molecular subgroup can be found in **Table 1**.

CMS Status: Patients were identified as having developed CMS based on review of perioperative neuro-oncology and/or neuro-surgery notes stating that the patient had CMS and/or by documented neurologic exams noting mutism and at least one other symptom of CMS. CMS was defined as per the recent Delphi consensus conference.[1]

Tumor Location and Volume: Tumor location was classified as either midline or lateral on review of axial T2-weighted MRI. Tumor volume was calculated after measuring largest cranio-caudal, antero-posterior, and transverse diameters. Cranio-caudal diameter was measured on sagittal T1-weighted MRI, antero-posterior diameter and transverse diameter were measured on axial T2-weighted MRI. All patients from LPCH, HSC and GOSH were imaged on a 1.5T or 3T scanner. (LPCH: Signa or Discovery 750, GE Healthcare; HSK: Signa, GE Healthcare; Achieva, Philips Healthcare Best, the Netherlands; Avanto, Siemens, Erlangen, Germany. GOSH: 1.5T Avanto, Siemens, Erlangen, Germany or 3T Prisma, Siemens, Erlangen, Germany).

Molecular subgrouping: Medulloblastoma subgroup determination of HSC, GOSH and LPCH patients was performed as previously described using nanoString limited gene expression profiling and/or Illumina genome wide methylation arrays.[21-23]

Statistical Methods: Statistical analyses were performed using GraphPad Prism (version 8.0, GraphPad Software Inc., San Diego, CA) and R Statistical Software (v3.3.3) with an a priori significance level of $P<0.05$. Categorical variables (midline location, gender, CMS) were compared across subgroups and within subgroups stratified by CMS status using Chi-square test. Continuous variables (age and volume) were compared across subgroups using Kruskal-Wallis test. Mann-Whitney test was used to compare differences in continuous variables (age and volume) stratified by CMS status within subgroups.

Results:

Patient Characteristics by CMS Status

Overall, we found that 25.9% of our patients developed CMS (**Table 2**). Patients who developed CMS were diagnosed with medulloblastoma at a younger age (mean difference -2.73 years ± 0.8, $P=0.0027$). There was no difference in gender between patients who developed CMS and those who did not ($P=.9354$). CMS patients had tumors with greater volumes (mean difference 16.99 cm^3 ± 5.287, $P<0.0001$) that were more often located midline ($OR=20.03$, $P<0.0001$).

Patient Characteristics by Medulloblastoma Subgroup

CMS incidence varies significantly by subgroup (P=0.0013) (**Figure 1A**). Group 4 patients had the highest rate of CMS with 39% of patients developing the postoperative complication. Group 3 patients followed closely behind at 33%. SHH patients had the lowest rate of CMS at 7%. WNT patients had an intermediate rate of CMS standing at 24% (**Table 1**). Age at diagnosis was found to vary significantly among the different subgroups (P<0.0001) with WNT tumors presenting at older age (median=10.87) followed by Group 4 (median=9.00) and Group 3 or 4 (median=9.00), SHH (median=7.00), and Group 3 (median=4.70). Within subgroups, only in WNT (P=0.41) and Group 3 or 4 (P=0.034) tumors did younger age at diagnosis increase risk for CMS (**Figure 1B**). There were no significant differences in gender distribution and tumor volume among the different subgroups. Within subgroups, greater tumor volume increased risk of CMS among WNT (P=0.034), Group 3 (P=0.0099), and Group 4 (P=0.00003) patients (**Figure 1C**).

Multivariable Analysis of Risk Factors

On multivariable analysis we found that WNT (adjusted odds ratio=5.06, P=0.027) and Group 4 (adjusted OR=7.42, P=0.004) tumor subgroups independently increase the risk of CMS as compared to SHH subgroup (**Table 3**). Group 3 subgroup reached the threshold of statistical significance (adjusted odds ratio=3.86, P=0.058). Tumor volume increased risk of CMS in a linear fashion with tumors between 50 and 100cm^3 having an adjusted odds ratio of 3.88 (P=0.002) and tumors greater than 100cm^3 having an adjusted odds ratio of 6.81 (P<0.001) as compared to tumors less than 50cm^3. Older age decreased the risk of CMS (adjusted odds ratio 0.89, P=0.025). Midline location reached

borderline significance with an adjusted odds ratio of 7.01 (P=0.079). Gender did not affect risk of CMS.

Discussion

Herein we show in the largest molecularly characterized medulloblastoma cohort to date that molecular subgroup is a strong predictor of CMS. Our study suggests that many of the previous risk factors identified for CMS, specifically midline location, younger age and increased tumour volume are likely reflections of underlying subgroup. Moreover, by incorporating molecular subgroup we have been able to develop a more robust model of prediction of CMS.

Our finding that SHH medulloblastoma are at low risk for the development of CMS is consistent with previous observations that midline tumours are at much higher risk for development of CMS.[4,7,24] Indeed, we and others have previously shown that almost all SHH medulloblastoma are not in the 4th ventricle rather within the cerebellum itself, pertaining to disparate cell of origins between the four groups. Specifically, SHH arise from the external granule layer, while WNT arise from the lower rhombic lip, Group 3 arise from Nestin+ cells, and Group 4 from the unipolar brush cells.[13] This is supported by the four cases of CMS in SHH that we observed were arising from the vermis.[16,19] This is consistent the previous hypotheses that the putative cause of CMS is an increased splay of the superior cerebellar peduncles resulting in post-surgical swelling and disruption of the proximal dentatothalamocortical pathway.[7] Indeed, our findings of large volume WNT and Group 4 tumours being at highest risk for CMS are consistent with this finding, including our previous observations that WNT and Group 4 have very long pre-diagnostic

intervals compared to SHH and Group 3.[12] This suggests that slow growing, large midline tumours are possibly at highest risk for development of CMS.

Our multivariable regression model shows that even when accounting for age, volume and midline location, WNT and Group 4 tumours have a significantly increased risk of developing CMS. Previously we have shown that radio-genomics can be applied to predict subgroup pre-operatively, specifically, SHH tumours are almost always cerebellar and Group 4 tumours are 4th ventricular tumours which do not enhance.[14,16,25] WNT tumours are frequently arising from the lateral recess. Alternatively, previous reports that surgical approach is not a statistically significant predictor of the development of CMS were not subgroup specific, and as such, it is possible that alternate peri-operative strategies may be effective when enriching for the highest risk groups. [3,8,26,27] The emergence of pharmacological interventions such as zolpidem and bromocriptine maybe possibly play a role pre-operatively or in the immediate post-operative period in the highest risk patients, although these interventions have not shown robust data in properly controlled prospective trials.[28-32] Indeed, we have recently shown that machine learning can be applied to predict subgroup on pre-operative imaging, suggesting incorporation of clinical variables such as risk of mutism could be done remotely, and consistently allowing for early intervention.[25]

This study has the classical limitations of a retrospectively collected cohort. However, there are unfortunately no robust prospective studies of predictors of CMS development, which has been a major limitation of all previous studies of CMS. Prospective evaluation of the development of CMS by cooperative groups with rigid inclusion criteria are required

to advance our understanding of this condition, with pre and post-operative speech language pathology assessments. Our results provide a robust framework for the prediction of the highest risk patients, and suggest that pre-operative or emerging intraoperative methods to determine molecular subgroup can allow for early identification of the highest risk patients.

Taken together, this study highlights another significant clinical difference between the four core medulloblastoma subgroups. Our work provides further insights into risk factors for CMS, and support potential mechanisms of its development, specifically perturbation of the cerebellar outflow tracts. These results are in line with our previous work suggesting that long-term outcomes have a subgroup specificity, and suggest that supportive care studies in medulloblastoma should also be conducted in a subgroup specific manner. Future studies of CMS risk in medulloblastoma should incorporate molecular subgroup, opening up a potential new avenue of robust pre-operative prediction.

Funding: Funding for this work was provided by operating funds from the Canadian Institutes of Health Research, American Brain Tumor Association, the Garron Family Cancer Center, Meagan's Walk, b.r.a.i.n.child, Nelina's Hope, the C.R. Younger Foundation and the Brain Tumour Foundation of Canada to VR. A Long term international fellowship from the Conquer Cancer Foundation to NA. Funds from the Lucile Packard Children's Foundation Brain & Behavior Center Award in Pediatric Neurosciences to KY. Funds from the Pediatric Brain Tumor Foundation, Canadian Institutes for Health Research and National Institutes of Health to MDT.

References:

1. Gudrunardottir T, Morgan AT, Lux AL, et al. Consensus paper on post-operative pediatric cerebellar mutism syndrome: the Iceland Delphi results. *Childs Nerv Syst.* 2016; 32(7):1195-1203.

2. Robertson PL, Muraszko KM, Holmes EJ, et al. Incidence and severity of postoperative cerebellar mutism syndrome in children with medulloblastoma: a prospective study by the Children's Oncology Group. *J Neurosurg.* 2006; 105(6 Suppl):444-451.

3. Pollack IF, Polinko P, Albright AL, Towbin R, Fitz C. Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. *Neurosurgery.* 1995; 37(5):885-893.

4. Law N, Greenberg M, Bouffet E, et al. Clinical and neuroanatomical predictors of cerebellar mutism syndrome. *Neuro Oncol.* 2012; 14(10):1294-1303.

5. Moxon-Emre I, Bouffet E, Taylor MD, et al. Impact of Craniospinal Dose, Boost Volume, and Neurologic Complications on Intellectual Outcome in Patients With Medulloblastoma. *J Clin Oncol.* 2014.

6. Moxon-Emre I, Taylor MD, Bouffet E, et al. Intellectual Outcome in Molecular Subgroups of Medulloblastoma. *J Clin Oncol.* 2016; 34(34):4161-4170.

7. Morris EB, Phillips NS, Laningham FH, et al. Proximal dentatothalamocortical tract involvement in posterior fossa syndrome. *Brain.* 2009; 132(11):3087-3095.

8. Renne B, Radic J, Agrawal D, et al. Cerebellar mutism after posterior fossa tumor resection in children: a multicenter international retrospective study to determine possible modifiable factors. *Childs Nerv Syst.* 2019.

9. Nor C, Ramaswamy V. Clinical and pre-clinical utility of genomics in medulloblastoma. *Expert Rev Neurother.* 2018; 18(8):633-647.

10. Ramaswamy V, Taylor MD. Medulloblastoma: From Myth to Molecular. *J Clin Oncol.* 2017; 35(21):2355-2363.

11. Ramaswamy V, Remke M, Bouffet E, et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. *Acta Neuropathol.* 2016; 131(6):821-831.

12. Ramaswamy V, Remke M, Adamski J, et al. Medulloblastoma subgroup-specific outcomes in irradiated children: who are the true high-risk patients? *Neuro Oncol.* 2016; 18(2):291-297.

13. Vladoiu MC, El-Hamamy I, Donovan LK, et al. Childhood cerebellar tumours mirror conserved fetal transcriptional programs. *Nature.* 2019.

14. Perreault S, Ramaswamy V, Achrol AS, et al. MRI surrogates for molecular subgroups of medulloblastoma. *AJNR Am J Neuroradiol.* 2014; 35(7):1263-1269.

15. Wefers AK, Warmuth-Metz M, Poschl J, et al. Subgroup-specific localization of human medulloblastoma based on pre-operative MRI. *Acta Neuropathol.* 2014; 127(6):931-933.

16. Mata-Mbemba D, Zapotocky M, Laughlin S, Taylor MD, Ramaswamy V, Raybaud C. MRI Characteristics of Primary Tumors and Metastatic Lesions in Molecular Subgroups of Pediatric Medulloblastoma: A Single-Center Study. *AJNR Am J Neuroradiol.* 2018.

17. Zapotocky M, Mata-Mbemba D, Sumerauer D, et al. Differential patterns of metastatic dissemination across medulloblastoma subgroups. *J Neurosurg Pediatr.* 2018; 21(2):145-152.
18. Patay Z, DeSain LA, Hwang SN, Coan A, Li Y, Ellison DW. MR Imaging Characteristics of Wingless-Type-Subgroup Pediatric Medulloblastoma. *AJNR Am J Neuroradiol.* 2015; 36(12):2386-2393.
19. Ramaswamy V, Remke M, Shih D, et al. Duration of the pre-diagnostic interval in medulloblastoma is subgroup dependent. *Pediatr Blood Cancer.* 2014; 61(7):1190-1194.
20. Raybaud C, Ramaswamy V, Taylor MD, Laughlin S. Posterior fossa tumors in children: developmental anatomy and diagnostic imaging. *Childs Nerv Syst.* 2015; 31(10):1661-1676.
21. Hovestadt V, Remke M, Kool M, et al. Robust molecular subgrouping and copy-number profiling of medulloblastoma from small amounts of archival tumour material using high-density DNA methylation arrays. *Acta Neuropathol.* 2013; 125(6):913-916.
22. Northcott PA, Shih DJ, Remke M, et al. Rapid, reliable, and reproducible molecular sub-grouping of clinical medulloblastoma samples. *Acta Neuropathol.* 2012; 123(4):615-626.
23. Cavalli FMG, Remke M, Rampasek L, et al. Intertumoral Heterogeneity within Medulloblastoma Subgroups. *Cancer Cell.* 2017; 31(6):737-754.e736.
24. Liu JF, Dineen RA, Avula S, et al. Development of a pre-operative scoring system for predicting risk of post-operative paediatric cerebellar mutism syndrome. *Br J Neurosurg.* 2018; 32(1):18-27.
25. Iv M, Zhou M, Shpanskaya K, et al. MR Imaging-Based Radiomic Signatures of Distinct Molecular Subgroups of Medulloblastoma. *AJNR Am J Neuroradiol.* 2019; 40(1):154-161.
26. Thompson EM, Bramall A, Herndon JE, 2nd, Taylor MD, Ramaswamy V. The clinical importance of medulloblastoma extent of resection: a systematic review. *J Neurooncol.* 2018.
27. Thompson EM, Hielscher T, Bouffet E, et al. Prognostic value of medulloblastoma extent of resection after accounting for molecular subgroup: a retrospective integrated clinical and molecular analysis. *Lancet Oncol.* 2016; 17(4):484-495.
28. Shyu C, Burke K, Souweidane MM, et al. Novel use of zolpidem in cerebellar mutism syndrome. *J Pediatr Hematol Oncol.* 2011; 33(2):148-149.
29. Brefel-Courbon C, Payoux P, Ory F, et al. Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. *Ann Neurol.* 2007; 62(1):102-105.
30. Clauss R, Nel W. Drug induced arousal from the permanent vegetative state. *NeuroRehabilitation.* 2006; 21(1):23-28.
31. Adachi J, Nishikawa R, Hirose T, Matsutani M. Mixed neuronal-glial tumor of the fourth ventricle and successful treatment of postoperative mutism with bromocriptine: case report. *Surg Neurol.* 2005; 63(4):375-379.
32. Caner H, Altinors N, Benli S, Calisaneller T, Albayrak A. Akinetic mutism after fourth ventricle choroid plexus papilloma: treatment with a dopamine agonist. *Surg Neurol.* 1999; 51(2):181-184.

Figure Captions:

Figure 1. A: Proportion of cases developing CMS by medulloblastoma subgroup. P=0.0013 (Chi-square test). **B:** Age at diagnosis in years stratified by medulloblastoma subgroup and CMS status. Boxes represent median and interquartile range and whiskers represent 10-90% confidence intervals (Mann-Whitney Test). **C:** Tumor volume in cm^3 stratified by medulloblastoma subgroup and CMS status. Boxes represent median and interquartile range and whiskers represent 10-90% confidence intervals (Mann-Whitney Test).