Neuro-Oncology 12(12):1311–1317, 2010.
doi:10.1093/neuonc/noq094
Advance Access publication August 16, 2010

Neurocognitive outcome 12 months following cerebellar mutism syndrome in pediatric patients with medulloblastoma

Shawna L. Palmer, Tim Hassall, Karen Evankovich, Donald J. Mabbott, Melanie Bonner, Cinzia Deluca, Richard Cohn, Michael J. Fisher, E. Brannon Morris, Alberto Broniscer, and Amar Gajjar

Departments of Behavioral Medicine (S.L.P.); and Oncology (E.B.M., A.B., A.G.), St. Jude Children's Research Hospital, Memphis, Tennessee; Royal Children's Hospital, Brisbane, Queensland, Australia (T.H.); Texas Children's Hospital, Houston, Texas (K.E.); The Hospital for Sick Children, Toronto, Canada (D.J.M.); Duke University Medical Center, Durham, North Carolina (M.B.); Royal Children's Hospital, Melbourne, Victoria, Australia (C.D.); Sydney Children's Hospital, Sydney, New South Wales, Australia (R.C.); Children's Hospital of Philadelphia, Philadelphia, Pennsylvania (M.J.F.)

The aim is to prospectively assess early neurocognitive outcome of children who developed cerebellar mutism syndrome (CMS) following surgical resection of a posterior fossa embryonal tumor, compared with carefully matched control patients. Children who were enrolled on an ongoing IRB-approved protocol for treatment of embryonal tumors, were diagnosed with postoperative CMS, and had completed prospectively planned neuropsychological evaluation at 12 months postdiagnosis were considered eligible. The cognitive outcomes of these patients were examined in comparison to patients without CMS from the same treatment protocol and matched with regard to primary diagnosis, age at diagnosis, and risk/corresponding treatment ($n = 22$ pairs). Seventeen were also matched according to gender, and 14 were also matched according to race. High-risk patients received 36–39.6 Gy CSI and 3D conformal boost to the primary site to 55.8–59.4 Gy. Average-risk patients received 23.4 Gy CSI and 3D conformal boost to the primary site to 55.8 Gy. Significant group differences were found on multiple cognitive outcomes. While the matched control patients exhibited performance in the average range, patients who developed CMS postsurgery were found to have significantly lower performance in processing speed, attention, working memory, executive processes, cognitive efficiency, reading, spelling, and math. Patients treated for medulloblastoma who experience postoperative CMS show an increased risk for neurocognitive impairment, evident as early as 12 months following diagnosis. This study highlights the need for careful follow-up with neuropsychological evaluation and for obtaining critical support for patients and their families.

Keywords: cerebellar mutism, medulloblastoma, posterior fossa syndrome.

Treatment for pediatric embryonal tumors includes surgery, craniospinal irradiation (CSI), and adjuvant chemotherapy, resulting in an 85% 5-year survival rate among those children with standard risk disease and 70% among those considered high risk.[1] These survivors are at high risk for developing adverse posttreatment sequelae, with extensive and long-term neurocognitive deficits being well documented in the literature.[2–12] Deficits have often been attributed to the detrimental impact of radiation dose exposure to healthy brain tissue. In order to reduce these lasting treatment-related effects, modern treatment trials have aimed to reduce the dosage of cranial radiation therapy or, in the case of young children, to delay the need for radiation therapy with chemotherapy. Surgery remains the first phase of treatment for almost all patients and concerns regarding surgery-related complications exist.[13,14] Following surgical resection, but prior to treatment by other modalities, up to 29% of patients develop cerebellar mutism syndrome (CMS), a

Received February 26, 2010; accepted July 2, 2010.

Corresponding Author: Shawna L. Palmer, PhD, Department of Behavioral Medicine, MS 740, St Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105–2794 (shawna.palmer@stjude.org).

postoperative clinical entity characterized by diminished or absent speech, ataxia, hypotonia, and emotional lability.[13,15,16] Additional symptoms, including difficulties with verbal comprehension, apathy, lack of initiative, and persistent eye closure, have also been reported.[17] Symptoms have been documented to arise 0–11 days (mean, 1.5 days) following surgery,[18] and are also highly variable with regard to severity (ranging from mild to severe)[19] and nature (transient to unresolving).[18,20–22]

While neurocognitive late effects among pediatric embryonal tumor survivors are well described, many of the current reports that include such assessments either exclude patients with CMS from analyses or group these patients together with those who do not develop CMS when describing outcomes. In addition, the development of CMS makes it very difficult, if not impossible, to conduct valid neuropsychological assessment until symptoms subside. Of the few studies that do exist, most have been retrospective in nature[17,22,23] or have concentrated on monitoring speech and language.[22–24] Studies reporting formal neuropsychological testing of patients with CMS are rare.[25] In 2000, the neuropsychological function of a subgroup of six children diagnosed with CMS following surgery was presented.[25] However, this report also emphasized speech and language and did not include a comparison between patients with and without CMS. In 2006, the Children's Oncology Group presented a broad examination of 450 children with medulloblastoma, of which 24% developed CMS. Unfortunately, the report of perceived cognitive deficits included only average-risk patients and information was derived from written notes on a follow-up form, providing an estimation of function by the attending physician, rather than a direct formal evaluation. Judged impairment was categorized as none, mild, moderate, or severe with no reference to how these categorizations were determined. As a result, a clear understanding of the neuropsychological deficits faced specifically by those with CMS following surgery remains elusive.

The aims of the current study are (i) to prospectively assess the neurocognitive performance of those children who developed CMS following surgical resection of a posterior fossa embryonal tumor utilizing protocol-driven formal testing methods, and (ii) to compare the performance of those with CMS with that of disease, treatment, and demographically matched controls.

Methods

Patients and Procedures

Study participants were recruited from an ongoing multisite IRB-approved clinical trial for patients newly diagnosed with an embryonal tumor. Written informed consent was obtained for participation. At the time of the study, 283 patients were enrolled on the protocol. Of these, 49 (17.3%) had developed postsurgical CMS. Thirty-seven of these 49 patients were at least 12 months postdiagnosis. At 12 months following diagnosis, all patients were prospectively scheduled for neuropsychological evaluation. However, 10 of the 37 patients did not complete evaluation due to language barriers restricting neuropsychological assessment ($n = 1$), progressive disease and off study ($n = 1$), expired ($n = 1$), parent refusal ($n = 1$), not physically well enough to be assessed ($n = 5$), and missed appointment ($n = 1$). Although assessed, 2 additional patients were excluded due to having received a cognitive intervention aimed at improving performance as part of a separate rehabilitation study.

Matching—Twenty-five patients who had developed CMS were eligible to be matched with patients who did not develop CMS but who were enrolled on the same treatment protocol. Matching took place according to 3 critical risk factors established in previous literature:[2–12] (i) primary diagnosis, (ii) risk/corresponding treatment (HR or AR), and (iii) age at diagnosis. Unfortunately, based on these strict criteria, no match existed for 3 CMS patients. Therefore, 22 pairs were included in the study group; 22 CMS patients and 22 same-age control patients (Table 1). Seventeen pairs were also matched according to gender, 14 according to race, 17 according to primary tumor location, and 13 with regard to extent of resection.

Table 1. Patient demographics

	CMS ($n = 22$)	Controls ($n = 22$)
Age at diagnosis: mean (*SD*)	8.53 (3.1)	8.47 (3.1)
Risk (average:high)	16:6	16:6
Gender (male:female)	17:5	16:6
Race		
White	17	16
Black	0	2
Asian	2	2
Other	3	2
Primary tumor location		
4th ventricle	20	18
Left cerebellum	0	4
Cerebellar vermis	1	0
Cerebellar peduncle	1	0
Extent of resection		
GTR	12	17
NTR	8	4
STR	2	1
Brainstem invasion (yes:no)	8:14	2:20
Parent demographics		
Age: mean (*SD*)	37.1 (7.1)	37.7 (5.9)
Education: mean (*SD*)	13.3 (2.7)	14.2 (2.7)
Marital status		
Married	18	17
Divorced	0	4
Separated	3	0
Single	1	0

GTR, gross total resection; NTR, near total resection; STR, subtotal resection.

***Diagnosis and Treatment*—**Patients were diagnosed following pathologic review of resected tissue. All patients included in the study received the primary diagnosis of medulloblastoma and were treated with postsurgical risk-adapted CSI followed by 4 cycles of high-dose chemotherapy (cyclophosphamide, cisplatin, vincristine) with stem cell support as described previously.[1] High-risk patients received CSI to 36–39.6 Gy and conformal boost treatment of the primary site to 55.8–59.4 Gy. Average-risk patients received CSI to 23.4 Gy, conformal boost treatment to the primary site to 55.8 Gy.

***Neurocognitive Assessment*—**Patients enrolled on protocol are prospectively scheduled for neuropsychological evaluation at multiple time points, including Baseline, 1, 3, and 5 years thereafter. The large majority of those who develop CMS following surgery are not able to complete a valid assessment at Baseline. Therefore, 12 months postdiagnosis was chosen as the first comparison point for the current study.

Neuropsychological evaluation included the following measures: Woodcock–Johnson (WJ) Tests of Cognitive Abilities and Tests of Achievement (third edition),[26,27] Behavioral Rating Inventory of Executive Function,[28] and the Child Behavior Checklist (CBCL).[29] The WJ III Tests of Cognitive Abilities[27] is designed to assess a wide spectrum of both broad and narrow cognitive abilities. Each subtest provides a measure of a narrow ability, which can be then combined with other subtest scores to obtain a measure of a more broad ability, in the form of a factor or clinical cluster score. Thirteen subtests were administered providing clinical measures of general intellectual ability, processing speed, attention, working memory, executive processes, cognitive efficiency, auditory processing, phonemic awareness, spatial relations, and visual auditory learning. The WJ III Tests of Achievement[26] was developed to measure the major aspects of academic achievement. Twenty-two subtests were administered providing measures of oral language, verbal comprehension, broad reading, reading comprehension, spelling, math calculation, and mathematical reasoning. Standard scores are used on both the Tests of Cognitive Abilities and Achievement and have a population mean of 100 and a standard deviation of 15. Performance that derives standard scores between 120 and 111 is considered high average, 110 and 90 average, 89 and 80 low average, 79 and 70 low, and $<$69 very low.

Information on parent gender, marital status, and years of education was also collected. In addition, parents were asked to complete two paper and pencil instruments measuring aspects of their child's behavior; the Behavior Rating Inventory of Executive Function (BRIEF),[28] and the CBCL.[29] The BRIEF is a questionnaire providing a measure of 8 areas of executive function including the ability to resist impulses (inhibition), make transitions and tolerate change (shifting), appropriately express and regulate emotion (emotional control), begin a task or activity without prompting (initiation), hold and manipulate information (working memory), decide on appropriate steps in order to reach a goal (planning), maintain order in work, play or storage space (organization), and being self-aware (monitoring). The CBCL measures the parent's perspective on their child's activities, social relations, and school competence (activities, social, and school), and specific behavioral and emotional problems (internalizing, externalizing, aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed). Both measures result in *t*-scores with a population mean of 50 and a standard deviation of 10.

Statistical Procedures

Descriptive statistics were obtained to examine each group's cognitive performance. Paired samples *t*-tests were used to compare the cognitive outcomes of those who developed CMS to their matched controls without CMS. The procedure computes the differences between values for each pair and tests whether the average differs from 0 (indicating no difference between groups). Both patients in each pair were required to have complete data to be included in the analysis. Therefore, the number of pairs for each outcome varied. The *P*-value used to determine statistical significance in group differences was reduced to $<$.01 to adjust for multiple comparisons.

Despite careful matching, the groups differed with regard to extent of resection and brainstem invasion. Therefore, analyses of covariance were completed for each cognitive outcome, with extent of resection and brainstem invasion as covariates.

An analysis of effect size for each of the broad measures of cognitive ability and academic achievement, using the Cohen's d' statistic, was also completed to ascertain whether sufficient statistical power was available given the specific number of patients in our present study.

Results

Neurocognitive Outcomes

***Tests of cognitive abilities*—**Those patients who had developed CMS exhibited lower performance compared with those who had not on each of the cognitive ability measures. Significant differences ($P < .01$) were found on measures of general intellect, processing speed, broad attention, working memory, executive processes, cognitive efficiency, auditory processing, and spatial relations (Table 2). A trend toward a significant difference was evident on measures of phonemic awareness with the CMS group performing in the average range and the controls in the high average range. A trend toward a significant difference was also evident on measures of visual auditory learning with the CMS group performing in the low average range and the controls in the average range.

Analyses of covariance, with extent of resection and brainstem invasion as covariates, were also completed for the cognitive outcomes. Neither covariate was found to be a significant predictor for any outcome.

Table 2. Group differences in cognitive outcome with paired sample *t*-tests on standard scores (norm $M = 100$, $SD = 10$)

Cognitive outcome	Pairs	CMS patients		Control patients		Paired comparison	
	n	*M*	*SD*	*M*	*SD*	*t*	*P*-value
General intellectual ability	14	85.3	9.8	105.1	16.1	3.68	.003
Processing speed	16	63.5	18.6	92.0	15.0	5.11	<.001
Broad attention	15	73.6	19.6	103.4	17.8	5.36	<.001
Working memory	18	89.9	16.	107.7	18.3	3.02	.008
Executive processes	12	78.1	14.7	100.5	18.5	4.03	.002
Cognitive efficiency	18	70.6	21.5	98.0	18.1	4.59	<.001
Auditory processing	16	84.4	18.6	104.2	14.3	3.72	.002
Phonemic awareness III	13	96.9	14.8	112.6	19.5	2.64	.021
Spatial relations	19	90.2	15.6	108.0	17.5	4.03	.001
Visual auditory learning	18	82.0	23.1	101.1	13.5	2.49	.023

Table 3. Group differences in academic achievement with paired sample *t*-tests on standard scores (Norm $M = 100$, $SD = 10$)

Achievement outcome	Pairs	CMS patients		Control patients		Paired comparison	
	n	*M*	*SD*	*M*	*SD*	*t*	*P*-value
Oral language	19	87.3	15.7	106.8	13.3	4.18	.001
Verbal comprehension	21	93.0	19.6	107.6	15.5	2.71	.013
Broad reading	14	83.8	14.0	101.4	13.0	3.18	.007
Reading comprehension	10	91.7	13.8	102.2	13.2	1.91	.087
Spelling	20	85.7	24.1	106.1	11.5	3.63	.002
Math calculation skills	15	83.3	16.1	95.4	13.3	3.06	.008
Math reasoning	18	83.8	16.5	101.5	10.6	4.07	.001

After controlling for extent of resection and brainstem invasion, CMS group differences remained significant for processing speed ($F_{3,34} = 18.76$, $P < .001$) broad attention ($F_{3,30} = 10.49$, $P = .003$), working memory ($F_{3,35} = 9.02$, $P = .005$), executive processes ($F_{3,28} = 10.96$, $P = .003$), cognitive efficiency ($F_{3,35} = 12.93$, $P = .001$), auditory processing ($F_{3,33} = 10.11$, $P = .003$), and spatial relations ($F_{3,37} = 7.637$, $P = .009$).

Patients in the CMS group were found to demonstrate variable cognitive performance ranging from within average to more than 2.0 *SD* below population mean (Table 2). While general intellectual ability was found to be low average, working memory, phonemic awareness, and spatial relations were considered average. CMS patients demonstrated low average performance for auditory processing and visual auditory learning. Low performance was seen on broad attention skills, executive processes, and cognitive efficiency while processing speed showed the largest deficits and is considered very low performance.

Patients in the matched control group demonstrated consistently average performance on all outcomes with one exception (Table 2). Phonemic awareness was found to be in the high average range.

***Tests of achievement*—**Those patients who had developed CMS exhibited lower performance than those who had not on each measure of academic achievement. Significant matched group differences ($P < .01$) were found on measures of oral language, verbal comprehension, broad reading, math calculation, and mathematical reasoning (Table 3). Reading comprehension skills were not found to be significantly different between matched groups. A trend toward significant differences was found on verbal comprehension.

Analysis of covariance models, controlling for extent of resection and brainstem invasion, was also completed. Neither extent of resection nor brainstem invasion was found to be a significant predictor for any of the outcomes. CMS group differences remained significant for oral language ($F_{3,37} = 11.23$, $P = .002$) and math reasoning ($F_{3,35} = 7.76$, $P = .009$), but failed to be significant for verbal comprehension, broad reading, reading comprehension, spelling, and math calculation.

Both CMS and matched control group patients performed within the average range on measures of verbal and reading comprehension (Table 3). The matched controls also performed in the average range for the remaining academic measures. Those who had developed CMS performed in the low average range for oral language, broad reading, spelling, math calculation, and mathematical reasoning.

***Effect size*—**Large effect sizes ($d' \geq 0.80$) were evident for general intellect (0.98), processing speed (1.28), broad attention (1.38), executive processes (1.17), cognitive efficiency (1.08), auditory processing (0.93), oral language (0.96), broad reading (0.85), and math

reasoning (0.96). Medium effect sizes ($d' \geq 0.50–0.79$) were evident for working memory (0.71), phonemic awareness (0.73), reading comprehension (0.61), and math calculation (0.79). On the basis of these obtained effect sizes and the number of pairs available for each outcome, statistical power was calculated. Owing to the lack of the required observations, insufficient power to detect a difference between groups was found for phonemic awareness, broad reading, reading comprehension, and math calculation. All other outcomes had elevated and sufficient power (0.85–0.99).

Parent measures—Information from the parents of 22 CMS patients and 21 control patients was obtained. No significant differences were found between parents of patients who developed CMS and those who did not on years of education, age, or marital status (Table 1).

No significant differences were found between those who had developed CMS and those who did not on any measure derived from the BRIEF. Both patient groups were rated by their parents as in the average range on inhibition, shifting, emotional control, initiation, working memory, planning, organization, and monitoring.

Similarly, no significant differences were found on parent ratings of their children's behavior on the CBCL. However, trends toward significance were seen for those who had developed CMS to have lower school competence ($P = 0.03$) and an increase in social problems ($P = 0.05$) when compared with those who had not developed CMS.

Discussion

The current study utilizes prospectively planned psychological testing to evaluate the neurocognitive impact of developing CMS following surgery for embryonal tumors. Results reveal that at 12 months postdiagnosis, patients who develop CMS demonstrated multiple cognitive and achievement discrepancies compared with their matched control patients who did not develop CMS. Patients with CMS exhibited lower performance than their matched controls on each cognitive outcome assessed, with particular vulnerability in the areas of processing speed, attention, working memory, executive processes, cognitive efficiency, and auditory processing. This study is unique not only because of the careful matching process for purposes of comparison but also in the application of individual comprehensive assessment of multiple neurocognitive functions.

The current results clearly demonstrate that the development of postoperative CMS places the patient at increased risk for neurocognitive deficits quantifiable as early as 12 months postdiagnosis. Of the outcomes currently assessed, patients in both groups received their lowest score on processing speed. While those in the matched control group demonstrated average performance on processing speed, those in the CMS group showed critical slowing in the area of processing speed with a mean performance ($M = 63.5$) more than 2 *SD* below the norm (population mean = 100, $SD = 15$). The pathways by which processing speed and intelligence are related have been studied within a large healthy group of 214 children and adolescents.[30,31] Results support a developmental cascade model with age-related improvements in intelligence found to be related to improvements in processing speed. Additional analyses found that 97% of age-related improvement in working memory was accounted for by processing speed, and together working memory ability and processing speed accounted for 80% of age-related improvements in intelligence.[31] These results express the importance of processing speed on future and corresponding development of critical core cognitive abilities and general intellect. Slowed information processing speed may be the first deficit to emerge following treatment,[2,32] and based on the current results, those who develop CMS may be at higher risk for consequent deficits. Cognitive intervention development that focuses on improving, and/or accommodating for, slowed processing speed may well serve this population.

Parent questionnaires and surveys provide important insight into the family and caregiver experience and are often used in studies involving children. Interestingly, the current study found no significant differences in the parent ratings of child executive function and behavior. In 2005, a study of caregiver and patient self-report on perceived cognitive abilities was described.[33] Rather than relying solely on caregiver and self-report within clinical and research assessment, results demonstrated the importance of also including direct assessment. Both the survivors and their caregivers overestimated the survivor's neurocognitive abilities. Actual test scores were significantly lower on measures of overall cognitive ability, attention, memory, and problem solving. While it stands to reason that direct assessment methods provide a greater degree of measurement sensitivity, caregiver perspective remains a key source of information. The finding that parents of the patients with CMS underestimate the degree of deficit their child is experiencing is important and may be partially related to how mutism is described to the family and the lack of understanding, at least early in the illness, of how devastating this syndrome may be. Through parent report, the current results did showed a trend toward lowered school competence and difficulties with social skills for those with CMS when compared with those who did not develop CMS. Therefore, it is important to include measurement of these issues in risk-based assessment of this population.

The cause of CMS is of yet largely unknown and continues to be a heavily debated topic. The postoperative period when the patient exhibits normal speech and behavior, prior to the onset of CMS symptoms, contributes to the hypothesis that CMS is not a direct result of the tumor itself.[23] Development of postsurgical edema, ischemia, alterations in neurotransmitters, and degeneration of synaptic structures have been suggested as possible mechanisms to explain the delayed onset of CMS symptoms.[17,23] Recent studies, including those utilizing neuroimaging, have implicated the

dentatothalamocortical tracts, which stem from the dentate nuclei within the cerebellum and cross the midbrain tegmentum to reach the thalamus.[19,34–37] From the thalamus, connections are also made to the parietal cortex, prefrontal cortex, and superior temporal sulcus.[35,36] Rather than a discrete or localized injury at the site of the lesion, interruption to communication along these efferent cerebellar pathways may contribute to the onset of CMS symptoms and, consequently, to deficits in cognitive performance.[37]

While the current study is the first to report detailed neuropsychological outcomes among CMS patients, it is important to note the potential for bias within our patient groups. Of the 37 CMS patients who were at least 12 months following diagnosis, 10 did not receive the scheduled cognitive evaluation and were therefore excluded. Of these 10, 7 did not complete evaluation due to medical reasons (expired, $n = 1$; progressive disease, $n = 1$; and not feeling physically well enough to be assessed, $n = 5$). It may be that these 7 patients experienced the greatest severity of CMS symptoms following surgery. However, without prospective data on symptom type and severity, as well as patterns of recovery, it is impossible to ascertain the influence these variables may or may not have on neurocognitive outcome. Therefore, the lack of such data is considered a limitation of the study. It is imperative that careful collection of this information be included in future protocols.

A potential source of bias also stems from the matching process. Patients were matched with regard to critical cognitive risk factors; age at diagnosis, disease, and risk. Therefore, each pair received the same radiation treatment and chemotherapy regimen. Significant group differences due to radiation dose exposure and/or the impact of chemotherapy are therefore unlikely. However, it was impossible to match the pairs according to all variables resulting in some key differences between the CMS and Control groups. For example, 8 of the 14 patients in the CMS group were found to have brainstem involvement while only 2 of the 20 Control patients were found to have the same. Brainstem involvement may be an important factor and one to consider in future studies.

The current study implemented a cross-sectional approach. The poor medical status of those who develop CMS makes it difficult, if not impossible, for valid neuropsychological assessment to be completed at baseline. Therefore, studies of this population must wait until symptoms resolve to ensure the neuropsychological evaluation is a valid indication of the patient's ability. In order to extend our understanding of CMS late effects, longitudinal follow-up is also necessary to determine the relationship and timing of arising cognitive deficits. Both groups may continue a similar pattern of change in performance over time, with CMS patients remaining at a disadvantage. Alternatively, change over time may show a variable pattern of both gain and decline, and these patterns may be dependent on patient-related factors or the particular area of ability being studied.

In summary, this study highlights the importance of detailed risk-based neurocognitive assessment for patients who develop CMS following surgery. In addition to direct assessment, test batteries should also include parent report, especially with regard to their child's social and school competency. Rather than excluding CMS patients from subject cohorts, inclusion of detailed CMS recovery data from these patients would allow future research to examine how temporal patterns of recovery relate to neurocognitive outcome. Through ongoing research with enhanced methodology, these at-risk patients will gain accurate expectations regarding quality of survivorship. Continued monitoring and careful assessment will also provide the families with the required basis for obtaining efficacious support services, ultimately improving the quality of their survivorship.

Conflict of interest statement. None declared.

Funding

This work was supported in part by Cancer Center Support (CORE) grant P30CA21765 from the National Cancer Institute, The Noyes Brain Tumor Foundation, Musicians Against Childhood Cancer (MACC), and by the American Lebanese Syrian Associated Charities (ALSAC).

Acknowledgments

The authors would like to acknowledge Dana Wallace (St. Jude Children's Research Hospital), Michelle Swain (Royal Children's Hospital of Brisbane), Murali Chintagumpala (Texas Children's Cancer Center), Sridharan Gururangan (Duke University Medical Center), Eric Bouffet (The Hospital for Sick Children, Toronto), David Ashley (Royal Children's Hospital of Melbourne), Robyn Boyle (Sydney Children's Hospital), and Carol Armstrong (Children's Hospital of Philadelphia).

References

1. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol.* 2006;7:813–820.
2. Briere M, Scott JG, McNall-Knapp RY, et al. Cognitive outcome in pediatric brain tumor survivors: delayed attention deficit at long-term follow-up. *Pediatr Blood Cancer.* 2008;50:337–340.
3. Dennis M, Hetherington CR, Spiegler BJ. Memory and attention after childhood brain tumors. *Med Pediatr Oncol.* 1998;(Suppl 1):25–33.

4. Mabbott DJ, Penkman L, Witol A, et al. Core neurocognitive functions in children treated for posterior fossa tumors. *Neuropsychology*. 2008;22:159–168.
5. Mabbott DJ, Spiegler BJ, Greenberg ML, et al. Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. *J Clin Oncol*. 2005;23:2256–2263.
6. Mulhern RK, Palmer SL, Merchant TE, et al. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. *J Clin Oncol*. 2005;23:5511–5519.
7. Nagel BJ, Delis DC, Palmer SL, et al. Early patterns of verbal memory impairment in children treated for medulloblastoma. *Neuropsychology*. 2006;20:105–112.
8. Palmer SL, Gajjar A, Reddick WE, et al. Predicting intellectual outcome among children treated with 35–40 Gy craniospinal irradiation for medulloblastoma. *Neuropsychology*. 2003;17:548–555.
9. Palmer SL, Reddick WE, Gajjar A. Understanding the cognitive impact on children who are treated for medulloblastoma. *J Pediatr Psychol*. 2007;32:1040–1049.
10. Reeves CB, Palmer S, Gross AM, et al. Brief report: sluggish cognitive tempo among pediatric survivors of acute lymphoblastic leukemia. *J Pediatr Psychol*. 2007;32:1050–1054.
11. Spiegler BJ, Bouffet E, Greenberg ML, et al. Change in neurocognitive functioning after treatment with cranial radiation in childhood. *J Clin Oncol*. 2004;22:706–713.
12. Stargatt R, Rosenfeld JV, Maixner W, et al. Multiple factors contribute to neuropsychological outcome in children with posterior fossa tumors. *Dev Neuropsychol*. 2007;32:729–748.
13. Korah MP, Esiashvili N, Mazewski CM, et al. Incidence, risks, and sequelae of posterior fossa syndrome in pediatric medulloblastoma. *Int J Radiat Oncol Biol Phys*. 2010;77:106–112.
14. Packer RJ. Childhood medulloblastoma: progress and future challenges. *Brain Dev*. 1999;21:75–81.
15. Gajjar A, Sanford RA, Bhargava R, et al. Medulloblastoma with brain stem involvement: the impact of gross total resection on outcome. *Pediatr Neurosurg*. 1996;25:182–187.
16. 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;105:444–451.
17. Siffert J, Poussaint TY, Goumnerova LC, et al. Neurological dysfunction associated with postoperative cerebellar mutism. *J Neurooncol*. 2000;48:75–81.
18. De Smet HJ, Baillieux H, Catsman-Berrevoets C, et al. Postoperative motor speech production in children with the syndrome of "cerebellar" mutism and subsequent dysarthria: a critical review of the literature. *Eur J Paediatr Neurol*. 2007;11:193–207.
19. Wells EM, Walsh KS, Khademian ZP, et al. The cerebellar mutism syndrome and its relation to cerebellar cognitive function and the cerebellar cognitive affective disorder. *Dev Disabil Res Rev*. 2008;14:221–228.
20. Doxey D, Bruce D, Sklar F, et al. Posterior fossa syndrome: identifiable risk factors and irreversible complications. *Pediatr Neurosurg*. 1999;31:131–136.
21. Gelabert-Gonzalez M, Fernandez-Villa J. Mutism after posterior fossa surgery. Review of the literature. *Clin Neurol Neurosurg*. 2001;103:111–114.
22. Steinbok P, Cochrane DD, Perrin R, et al. Mutism after posterior fossa tumour resection in children: incomplete recovery on long-term follow-up. *Pediatr Neurosurg*. 2003;39:179–183.
23. Huber JF, Bradley K, Spiegler BJ, et al. Long-term effects of transient cerebellar mutism after cerebellar astrocytoma or medulloblastoma tumor resection in childhood. *Childs Nerv Syst*. 2006;22:132–138.
24. Vandeinse D, Hornyak JE. Linguistic and cognitive deficits associated with cerebellar mutism. *Pediatr Rehabil*. 1997;1:41–44.
25. Riva D, Giorgi C. The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. *Brain* 2000;123(Pt 5):1051–1061.
26. Woodcock R, McGraw K, Mather N. Woodcock–Johnson Third Edition, Tests of Cognitive Abilities. Itasca, IL: Riverside Publishing; 2001.
27. Woodcock R, McGraw K, Mather N. Woodcock–Johnson Third Edition, Tests of Achievement. Itasca, IL: Riverside Publishing; 2001.
28. Gioia GA, Isquith PK, Guy SC, et al. Behavior Rating Inventory of Executive Function. Lutz, FL: Psychological Assessment Resources, Inc.; 2000.
29. Achenbach TM, Rescorla LA. Manual for the ASEBA School-age Forms and Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families; 2001.
30. Fry AF, Hale S. Processing speed, working memory and fluid intelligence: evidence for a developmental cascade. *Psychol Sci*. 1996;7:237–241.
31. Fry AF, Hale S. Relationships among processing speed, working memory, and fluid intelligence in children. *Biol Psychol*. 2000;54:1–34.
32. Palmer SL. Neurodevelopmental impact on children treated for medulloblastoma: a review and proposed conceptual model. *Dev Disabil Res Rev*. 2008;14:203–210.
33. Maddrey AM, Bergeron JA, Lombardo ER, et al. Neuropsychological performance and quality of life of 10 year survivors of childhood medulloblastoma. *J Neurooncol*. 2005;72:245–253.
34. Charalambides C, Dinopoulos A, Sgouros S. Neuropsychological sequelae and quality of life following treatment of posterior fossa ependymomas in children. *Childs Nerv Syst*. 2009;25:1313–1320.
35. Baillieux H, De Smet HJ, Paquier PF, et al. Cerebellar neurocognition: insights into the bottom of the brain. *Clin Neurol Neurosurg*. 2008;110:763–773.
36. Morris EB, Phillips NS, Laningham FH, et al. Proximal dentatothalamocortical tract involvement in cerebellar mutism syndrome. *Brain*. 2009;132:3087–3095.
37. Miller NG, Reddick WE, Kocak M, et al. Cerebellocerebral diaschisis is the likely mechanism of postsurgical posterior fossa syndrome in pediatric patients with midline cerebellar tumors. *Am J Neuroradiol*. 2010;31:288–294.