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Posterior fossa syndrome in children following tumor resection: Knowledge update

Nisha Gadgil, Daniel Hansen, James Barry, Rocky Chang, Sandi Lam

Department of Neurosurgery, Baylor College of Medicine/Texas Children's Hospital, Houston, TX 77030, USA

E-mail: Nisha Gadgil - ngadgil@bcm.edu; Daniel Hansen - dxhansen@texaschildrens.org; James Barry - jamesbarrymd@gmail.com; Rocky Chang - rocky.chang@bcm.edu; *Sandi Lam - sklam@texaschildrens.org
*Corresponding author

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ILLUSTRATIVE CASES

Case 1

A 2-year-old female presented with a 2-month history of recalcitrant vomiting followed by ataxia and lethargy. Computed tomography (CT) scan of the head showed a large solid and cystic mass in the cerebellar vermis with severe hydrocephalus. Magnetic resonance imaging (MRI) demonstrated a 6.0 cm × 4.4 cm × 4.2 cm uniformly enhancing mass concerning for medulloblastoma with no evidence of spinal metastasis. She underwent external ventricular drain (EVD) placement and uneventful posterior fossa craniotomy with gross total resection of the lesion [Figure 1]. For surgical exposure, the lower two-thirds of the vermis was split in the midline. Pathology confirmed classic medulloblastoma M0. Postoperatively, the patient displayed mutism, left-sided dysmetria, truncal/gait ataxia, and mild generalized hypotonia. The patient had postoperative hydrocephalus and required ventriculoperitoneal (VP) shunt placement. Her mutism symptoms improved significantly by 1 month, with continuing speech therapy and occupational therapy. At her 2-month follow-up, she demonstrated persistent mild dysarthria, ataxia, and left-sided dysmetria. The patient completed high-dose chemotherapy and radiation therapy. At last follow-up, 45 months after tumor resection, she had entered age-appropriate first grade academics, but continues to have mild dysarthria, dysmetria, hypotonia, and wide-based gait.

Case 2

A 2-year-old boy presented with a 3-week history of progressive headache and daily vomiting. A CT scan revealed a solid mass in the fourth ventricle with moderate obstructive hydrocephalus. Presurgical MRI confirmed a 6.1 cm × 4.9 cm × 4.3 cm mass centered in the fourth ventricle and extending out the foramen of Luschka, consistent with an ependymoma. EVD placement and resection of the tumor were carried out in the same setting [Figure 2]. Posterior fossa craniotomy was performed and gross total resection was achieved; however, the tumor presented itself posteriorly and no splitting of the vermis was required. Cranial nerve monitoring was utilized due to the intimate nature of the tumor to the brainstem. Pathology was consistent with ependymoma. Postoperatively, the patient had complete mutism, but he otherwise demonstrated good neurologic function. Due to continued hydrocephalus, a VP shunt was placed several days after the original operation. By 2 months, the patient

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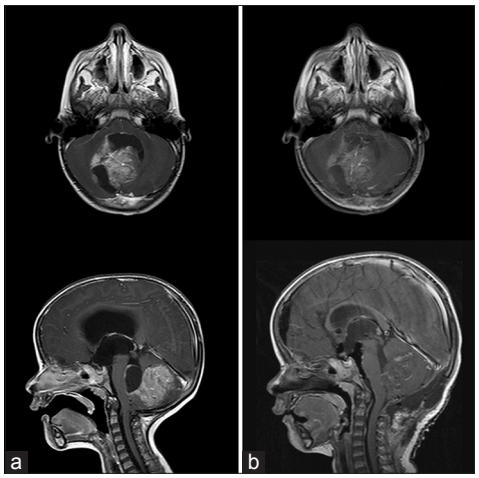

Figure 1: (a) Axial and sagittal T1 postcontrast magnetic resonance images. Large heterogeneous tumor, dorsal to the brainstem and occupying much of the posterior fossa with resulting obstructive hydrocephalus. (b) Postresection images in similar planes showing gross total resection of tumor and resulting decompression of brain stem and ventricular system

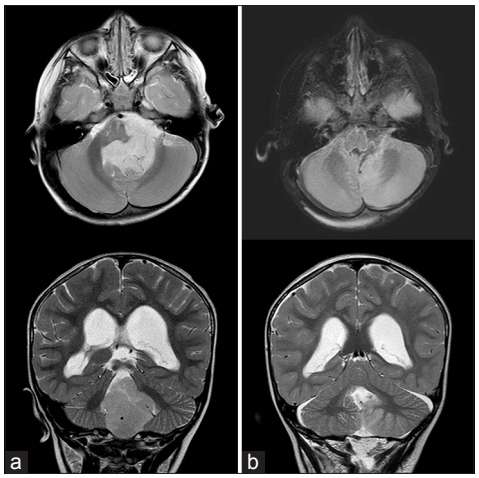

Figure 2: (a) Fluid-attenuated inversion recovery axial and T2 coronal magnetic resonance images. Large nonenhancing tumor, wrapping ventral to the brainstem and occupying the posterior fossa with resultant hydrocephalus. (b) Same sequence postresection images showing gross total resection of tumor, with mild reduction in ventricular caliber

was speaking a few words and by 6 months had returned to his age-appropriate neurologic baseline. He did receive proton beam radiation therapy to the tumor bed.

INTRODUCTION

Cerebellar mutism syndrome (CMS) refers to constellation of symptoms noted most commonly following surgery for posterior fossa tumors in the pediatric population. Mutism is a prominent, though not exclusive, characteristic of the syndrome and was first described in 1985 by Rekate *et al.*[27] In their paper, the authors described six children ranging from 1 to 6 years of age who developed complete absence of speech following resection of posterior fossa masses. Loss of speech was transient in all patients in this series, though many subsequent descriptions has been long lasting.[15,31,32] The term "syndrome" refers to a set of signs and symptoms observed to have correlation, but without clear understanding of underlying common pathogenesis. Although hundreds of articles now have been published describing what we commonly refer to as "posterior fossa syndrome," its unclear pathophysiology and pervasive consequences warrant further investigation.

CLINICAL PRESENTATION, EPIDEMIOLOGY, AND NATURAL HISTORY

CMS occurs in 8–24% of children following resection of posterior fossa masses.[24,29,35] Other uncommon though interesting pathophysiologic causes of this syndrome include trauma, strokes, and infection.[4,9,14,23] Rarely, CMS has been described in adults.[7,34] The syndrome is characterized most prominently by the absence or reduction in speech within 1–2 days of surgery without alteration in the level of consciousness.[6,12,28] Patients may retain the ability to produce speech immediately following surgery and become mute within an average of 2 days, but up to 7 days postoperatively.[12,29] Mutism is frequently accompanied by profound axial hypotonia and ataxia. One of the hallmarks of CMS is that long tract signs are not present; although hemiparesis has been described in the setting of CMS, the gradual return of motor function is typically accompanied by severe ataxia, suggesting that the paresis was, in fact, a result of cerebellar dysfunction.[15] Signs of brainstem dysfunction may be present, most commonly dysarthria,[28] dysphagia,[20] and abducens or facial nerve palsies. Mood lability or so-called "pseudobulbar affect,"[12,20,28] cognitive deficits,[28,37] and urinary incontinence or retention[33] may also be present. Poor oral intake and apathy are common. The syndrome has a broad spectrum of severity, ranging from mild to completely disabling symptoms.

The duration of mutism varies widely, with an average of approximately 8 weeks, but a range of 4 days to 5 months.[15] Although many consider CMS temporary due to the transience of mutism in most patients, the majority of patients experience persistent symptoms that may be debilitating. The pattern of speech return has been described in one long-term study as follows: Initially, the child speaks in single word and then progresses to full sentences. Speech is initially slow, quiet, and monotonous, with or without dysarthria. Long-term persistent dysarthria is common, and speech often remains slow and lacking in spontaneity.[29,32,39] This cerebellar ataxic dysarthria is primarily a motor impairment. Meta-analysis showed that even after the initial mutism had resolved, 68% of patients had residual

motor speech deficits a year after surgery.[15] Emotional lability is typically transient.[19] Other long-term sequelae include apraxia, ataxia, linguistic, memory, or behavioral disabilities.[15,31,32] Neuropsychological tests for children with CMS, compared to a control group, found statistically significant deficits in intellect, processing speed, attention, working memory, auditory processing, and spatial relations 12 months after surgery.[22] Functional prognosis correlates with the initial severity of symptoms as well as the duration of symptoms after surgery. Patients with mutism for greater than 4 weeks are at an increased risk of speech and language pathologies at 1-year follow-up.[17,29] In some cases, patients make rapid full recovery.[32]

ETIOLOGY AND PATHOPHYSIOLOGY

Despite collective efforts to describe the pathophysiological mechanism of CMS, the answer remains elusive. Several predisposing risk factors have been observed. Tumor pathology has proven the most predictive, with medulloblastoma patients experiencing a two- to three-fold increased chance of developing CMS as compared to other posterior fossa tumors.[5,15,39] Midline tumors, particularly those involving the vermis and those high in the fourth ventricle, present higher risk;[5,35] tumor involvement in or compression of the brainstem also carries a higher risk of postoperative CMS.[8,18,29] Some studies suggest that a vermian incision may pose a greater risk of CMS,[5,10] though this is not universally reported. Studies have shown conflicting results regarding the correlation of tumor size to the development of CMS.[5,15,29,38] Patients presenting with hydrocephalus in some series have a higher incidence of CMS,[36] though this has not been borne out in every study.[33] Patients with preoperative language impairment also have dramatically higher rates of CMS.[33] However, CMS occurs in only a subset of patients even with high preoperative similarity.

Although there is no clear consensus in the literature, many associate damage to the dentato-thalamo-cortical pathway with CMS.[12,19,25,28,36] The cerebral cortex delivers input to the cerebellum along the cortico-ponto-cerebellar pathway that eventually synapses on Purkinje cells of the cerebellum. These cells synapse on the deep cerebellar nuclei, from which efferent signals travel throughout the central nervous system. The dentate nuclei act as integration centers between the cerebellum and cortex, and they send efferent signals back to the cerebral cortex via dentate-thalamo-cortical pathway travelling through the superior cerebellar peduncle. This pathway plays a role in planned motor activity, coordination, and movement; it is also thought to modulate cognition and behavior. It is proposed that damage to efferent white matter pathways travelling through the superior cerebellar peduncle is responsible for CMS, particularly in cases of bilateral damage.[21,25] Damage to these pathways secondarily creates a phenomenon called diaschisis, in which cerebral cortical areas that receive input from cerebellar pathways become hypofunctional once input pathways are compromised. Two studies have shown that release of tumor tension from the superior cerebellar peduncle and subsequent inability to perceive the superior cerebellar peduncle white matter tracts on diffusion tensor imaging were predictive for the development of CMS.[18,21]

Damage to the vermis may also be important in the development of CMS. The vermis is implicated in speech initiation; while splitting of the inferior third of the vermis is not thought to increase CMS, damage to the superior vermis is considered to be a higher risk.[33] The vermis is posited to function like the limbic system of the cerebellum and is involved in complex social behavior mechanisms, emotions, and ability to plan. Puget *et al*. reported that the radiographic degree of damage to the dentate nuclei and the inferior vermis as seen on MRI directly correlates with the severity of cerebellar deficits.[26]

Bilateral dentate nuclei damage is also theorized to result in CMS, a theory backed by early work demonstrating mutism following stereotactic lysis of the dentate nuclei for dyskinesia.[13] The preponderance of midline tumors in CMS patients suggests involvement of the dentate nuclei in the development of this syndrome.

Direct damage to cerebellar neuronal pathways fails to explain why many patients are initially intact postoperatively and develop deficits after a few days, a finding that has led to speculation about other mechanisms. The onset of mutism coincides with the peak timing of postoperative edema;[25] some have reported that postoperative edema involving the dentate nuclei and progressive swelling of paramedian structures explains the delayed onset of mutism. However, edema alone fails to explain why deficits are frequently permanent.[22] Some authors have theorized that deficits in cerebellar perfusion caused by vascular manipulation or vasospasm may also account for the delay in the onset of symptoms.[2] While one study has found improvement of perfusion on single photon emission CT, correlated with improvement in symptoms,[12] others have directly refuted this theory.[8]

PREVENTION AND TREATMENT

To date, no specific treatment has been found for CMS other than supportive care. At our institution, many patients with this syndrome have been referred for intensive inpatient rehabilitation. Patients may require gastrostomy tube placement and intensive speech, physical, and occupational therapy. Although our outcomes have been positive, recovery is gradual and may

remain incomplete. For patients with primarily dysarthric speech disorders, exercises focused on coordination of sensorimotor integration should be emphasized. Other patients may have an apraxic language disorder, in which procedural memory and recognition of sensory stimuli is defective; this manifests in slow, monotone speech. Emphasis for these patients should be placed on the awareness of visual and auditory stimuli and planning of sound sequences.[33]

Several groups have reported single patient trials of pharmaceutical therapies for CMS, including steroids, fluoxetine, bromocriptine, or zolpidem.[1,3,11,30] While each had reported a positive result, the gradual improvement of the syndrome with time makes it difficult to attribute therapeutic effect to these medications.

Our lack of understanding of the precise pathophysiologic mechanism of CMS makes it difficult to accurately forecast which patients will develop the syndrome. While several predictive factors have been found, none can be used with certainty. Therefore, our hope at this time is prevention of damage from aggressive tumor resection.[15] In the face of malignant pediatric tumors, radical resections often confer superior prognosis. Some have proposed that a surgical approach that spares dissection of the vermis, specifically the telovelar approach, may reduce the risk of CMS. While one study using this method had no occurrences of CMS in 16 patients,[10] another found a postoperative incidence of CMS with this approach of 30% in a series of 20 patients.[40] CMS has been reported after both unilateral and bilateral telovelar dissections.[33] The relative importance of splitting the vermis versus damage to deep midline cerebellar structures from surgical manipulation is unclear. Hermann *et al.* proposed a transventricular supracerebellar approach to the fourth ventricle; in their series, there was no occurrence of CMS.[16] However, this approach may only be effective for tumors high in the fourth ventricle. Ultrasound-assisted surgery may assist in the safety of resections by decreasing the amount of retraction on cerebellar structures during exploration.[33] In summary, there are conflicting theories regarding the development of CMS; agreement across various studies is to avoid retraction and manipulation, particularly on deep midline cerebellar structures.

CONCLUSION

CMS is a common but devastating complication of posterior fossa surgery in children. While the mutism itself is often transient, permanent sequelae are common. The precise pathophysiology of this disease remains unknown, and treatment focuses on supportive care symptoms. At Texas Children's Hospital, multidisciplinary evaluation and treatment are integral to brain tumor care. Physical medicine and rehabilitation, neurology, ophthalmology, and neuro-oncology teams evaluate and follow patients; those with continuing therapy needs transition to intensive inpatient rehabilitation after surgery. Further investigation as to the underlying mechanism of CMS likely holds the promise of prevention and treatment of this syndrome.

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Conflicts of interest
There are no conflicts of interest.

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