DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS *14: 221–228 (2008)*

The Cerebellar Mutism Syndrome and Its Relation to Cerebellar Cognitive Function and the Cerebellar Cognitive Affective Disorder

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The postoperative cerebellar mutism syndrome (CMS), consisting of diminished speech output, hypotonia, ataxia, and emotional lability, occurs after surgery in up to 25% of patients with medulloblastoma and occasionally after removal of other posterior fossa tumors. Although the mutism is transient, speech rarely normalizes and the syndrome is associated with long-term adverse neurological, cognitive, and psychological sequelae. The clinical, neuroradiographic, and neuropsychological findings associated with CMS as well as possible mechanisms of injury are reviewed. Theories about the pathophysiology of CMS have evolved along with our understanding of the cerebellum as an important structure in the distributive neurocircuitry underlying complex speech, cognition, and behavior. CMS shares many similarities with the cerebellar cognitive affective syndrome, more commonly described in adults and consisting of disturbances of executive function, visuospatial skills, nonmotor language, and affect regulation. Future directions include more thorough neuropsychological characterization, functional and diffusion tensor imaging studies, and investigations into the underlying differences that may make some patients more vulnerable to CMS. Dev Disabil Res Rev 2008;14:221–228.

Key Words: cerebellar mutism; posterior fossa; cerebellar cognitive affective syndrome; medulloblastoma; cerebellum

INTRODUCTION

The postoperative cerebellar mutism syndrome (CMS) is a debilitating condition that develops in a subset patients who have undergone resection of posterior fossa tumors, including up to 25% of patients with medulloblastoma. Also referred to as the posterior fossa syndrome (PFS), CMS is characterized by severely diminished or absent speech output as well as other neurological, cognitive, and behavioral impairments. In addition to mutism, the most commonly observed findings are ataxia, hypotonia, and emotional lability. First described in 1979, CMS has been reported in over 300 cases to date [Gelabert-Gonzalez and Fernandez-Villa, 2001; Robertson et al., 2006]. Onset is typically 1–2 days postresection. Although the syndrome was previously considered transient, recent large scale studies reveal persistent features and poor long-term outcomes. To date, no demographic, clinical, or radiographic features consistently predict which patients will develop the syndrome. This manuscript will review the clinical, neuroradiographic, and neuropsychological findings associated with the syndrome, both at the time of diagnosis and at long-term follow-up. Theories concerning the pathophysiology and proposed mechanisms of injury, and the implications for cerebellar cognitive function will be discussed, as will the relationship to the cerebellar cognitive affective syndrome (CCAS), a chronic condition more commonly described in adults with cerebellar damage.

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Received 3 September 2008; Accepted 3 September 2008
Published online in Wiley InterScience (www.interscience.wiley.com).
DOI: 10.1002/ddrr.25

INCIDENCE

In case reports published in the 1980s and 1990s, CMS was usually described as rare. Single institution retrospective studies of postoperative CMS in children with posterior fossa tumors have found an incidence ranging from 2 to 40% [Van Calenbergh et al., 1995; Pollack, 1997; Robertson et al., 2006; De Smet et al., 2007]. A recent prospective study by the Children's Oncology Group (COG) of 450 children with medulloblastoma found CMS following tumor resection in 24% [Robertson et al., 2006]. Most cases of CMS occur following resection of posterior fossa tumors; however, it has also been described in other settings, both surgical and nonsurgical. Such cases include an acute subdural posterior fossa hematoma requiring excisions [Fujisawa et al., 2005], a cystic hemangioblastoma [Akil et al., 2006], an arteriovenous malformation of the vermis [Al-Anazi et al., 2001], posterior circulation infarction [Nandagopal and Krishnamoorthy, 2004], and acute cerebellitis [Papavasiliou et al., 2004]. The syndrome has been described in both pediatric and adult literature, but it is more common in children [Ildan et al., 2002].

CLINICAL FEATURES

In patients with CMS, loss of speech occurs without corresponding long tract signs, supranuclear or cranial nerve palsies. Most reports of postoperative CMS describe a latent phase of 1–5 days prior to the onset of symptoms, although in clinical practice early detection following surgery is difficult and onset is earlier in many patients, but poorly documented. Resolution of the muteness is often followed by a period of dysarthria [Van Calenbergh et al., 1995; Vadeinse and Hornyak, 1997; Riva and Giorgi, 2000]. Dysarthric speech in patients with cerebellar lesions has been described as loud, monotonous, scanning, slurring and with a slow rhythm and fluctuation of pitch, consistent with an ataxic dysarthria [Van Dongen et al., 1994; Ozimek et al., 2004].

Patients with CMS/PFS are present with several neurological, cognitive, and behavioral features in addition to the mutism and subsequent dysarthria. The most common neurological findings are ataxia and hypotonia. Recovery of gait and coordination is reported to take longer than speech [Siffert et al., 2000; Steinbok et al., 2003]. Oropharyngeal apraxia, hypokinesis, horizontal gaze paralysis, persistent eyelid closure, and vision loss without dysfunction of the third cranial nerve has also been reported [Dailey et al., 1995; Liu et al., 1998; Siffert et al., 2000; Ozgur et al., 2006]. Personality and emotional disturbances includes irritability, disinhibition, inattention, and lability of affect with poor cognitive and behavioral modulation [Levisohn et al., 2000; Robertson et al., 2006]. Cognitive impairment also occurs and will be discussed below.

Until recently, CMS was believed to be a transient phenomenon. Most early case studies describe the mutism as relatively brief, lasting days to months on average. In a 2001 review, mutism was described as transient in all 134 cases examined [Gelabert-Gonzalez and Fernandez-Villa, 2001]. However, the report did not characterize long-term speech and language outcomes or other neurological and cognitive features of CMS. More recent studies have demonstrated that while some aspects of the syndrome may be fleeting, persistent impairment is common, with complete recovery of speech and language being infrequent [Siffert et al., 2000; Steinbok et al., 2003; Huber et al., 2006; Robertson et al., 2006]. Motor speech deficits following the period of mutism have been identified, and the more chronic sequelae have been termed cerebellar mutism and subsequent dysarthria [De Smet et al., 2007]. Some of the associated behavioral disturbances have also been described as transient [Levisohn et al., 2000].

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More recent research suggests that the neurological and cognitive impairments in CMS often persist. A COG prospective study evaluated the neurological status of patients 1 year postdiagnosis based on the presence and severity of ataxia, language difficulties, and other cognitive deficits [Robertson et al., 2006]. Of the 46 patients who had postoperative CMS initially rated severe, residual deficits were common including 92% with ataxia, 66% with speech and language dysfunction, and 59% with global intellectual impairment. Of the 52 patients with moderate CMS, 78% had ataxia, 25% had speech and language dysfunction, and 17% had global intellectual impairment. Thus, impairment in these domains was common and was also directly related to the severity of CMS.

RISK FACTORS

Investigators have tried to identify risk factors in the development of CMS. Tumor type has been identified as a risk factor, with higher rates of CMS observed in medulloblastoma compared to other pediatric posterior fossa tumors. Vermal location has often been associated with the syndrome [Van Calenbergh et al., 1995; Grill et al., 2004], and in a 2001 review, 89% of 134 cases had the vermis as the tumor site [Gelabert-Gonzalez and Fernandez-Villa, 2001]. There has been no association between age and gender at the time of diagnosis and the development of CMS [Grill et al., 2004; Robertson et al., 2006; Turgut, 2008]. Although previous case studies indicated tumor size as a risk factor [Gelabert-Gonzalez and Fernandez-Villa, 2001], larger studies have not supported this theory [Robertson et al., 2006, Wells et al., in press]. Damage to the dentatothalaocortical outflow tracts from the cerebellar nuclei has also been identified as a possible risk factor. The COG study found that brainstem involvement was more likely to occur in patients with CMS compared to patients without CMS after resection of a posterior fossa tumor [Robertson et al., 2006]. Review of causation from a series of patients seen at the Children's National Medical Center revealed a trend, but no statistically significant associations between mutism and brainstem involvement [Wells et al., in press].

NEUROANATOMIC SUBSTRATE

CMS has been associated with lesions of the cerebellar vermis, lateral hemispheres, dentate nuclei, and the connections between these structures and the cerebral cortex. Much attention has been paid to the cerebellar vermis, because of the high frequency of midline tumors in patients with CMS and the absence of mutism in patients with large cerebellar hemispheric tumors that have been resected without directly involving the vermis [Grill et al., 2004]. However, resection of a vermian tumor does not necessarily lead to mutism. In

addition, CMS can result from damage to adjacent structures [Pollack et al., 1995]. The dentate nuclei are known to be involved in initiating voluntary movements, and damage to these paravermian structures is frequently seen in patients with CMS [Ozgur et al., 2006]. However, CMS does occur in the absence of edema or infarction in the dentate nuclei [Dailey et al., 1995], suggesting additional pathways. Other structures in the afferent and efferent pathways between the dentate nuclei and the premotor and supplementary motor cortices have also been implicated in the syndrome [Pollack et al., 1995; Koh et al., 1997; Ozgur et al., 2006].

NEURORADIOLOGIC STUDIES

Investigators have tried to determine whether neuroimaging may be used to predict the occurrence or outcome of CMS. Although case reports reveal postoperative damage in several neuroanatomic areas, no abnormality has been consistently found in CMS. A few systematic neuroimaging studies have compared patients with and without mutism, following posterior fossa tumor removal. Neither the size of the tumor, presence of hydrocephalus, nor the length of vermian incision was associated with the development of mutism [Robertson et al., 2006; Wells et al., in press].

The COG prospective study found that patients with CMS had more brainstem invasion compared to patients without CMS. There was also a negative correlation between CMS and cerebellar hemispheric tumors [Robertson et al., 2006]. Siffert et al. [2000] compared CT and MRI scans in eight children with CMS to eight unaffected children and found no distinguishing features. Pollack et al. performed a blinded comparison of CT or MRI scans of 12 patients with mutism to 24 cases of vermian tumors without mutism and found that bilateral edema within the cerebellar peduncles postoperatively was the only factor that was significantly associated with the mutism syndrome [Pollack et al., 1995]. These neuroimaging studies support the theory that the underlying neuoranatomical locus may be the dentatothalamocortical outflow tracts from the cerebellar nuclei through the brainstem. They suggest that the occurrence of CMS is not attributed to just one neuroanatomic region, but to any disruption of this neural circuitry.

Functional imaging of CMS is limited. A positron emission tomography (PET) study showed that patients with mutism may have decreased cerebral blood flow in the thalami, medial frontal lobes, temporal lobes, and cerebellar vermis [Sagiuchi et al., 2001]. However, in Pollack's study of 12 children experiencing CMS, PET was unremarkable [Pollack et al., 1995]. SPECT has demonstrated hypoperfusion in the left cerebellar hemisphere in a patient with CMS, and the radiographic abnormality resolved along with the mutism [Ersahin et al., 1996].

In a study currently being completed at the Children's National Medical Center, a variety of neuroradiographic features have been analyzed. This study suggests that CMS is associated with lasting postoperative damage to the cerebellum and brainstem, and this damage is not identified on immediate postoperative MRI [Wells et al., in press]. The changes include atrophy in all or parts of the cerebellar vermis and/or cerebellar hemispheres.

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CAUSE/MECHANISM OF INJURY

The mechanism of injury in postoperative CMS continues to be a matter of debate. Given the absence of symptoms preoperatively, damage from the tumor itself is unlikely. Possible mechanisms include direct injury from surgical trauma or vasospasm causing delayed injury to the cerebellar vermis, brainstem, dentate nuclei, or their projections.

Postsurgical edema from intraoperative manipulation has been suggested to be the principle mediator of cerebellar mutism. Some studies have shown increased edema in the cerebellum in patients with CMS [Dietze and Mickle, 1990; Ersahin et al., 1996]. The delayed onset of the speech impairment may reflect the time interval needed for edema to spread to the critical structures. Focal postoperative edema of the cerebellar peduncles and brain stem has been found to be a distinguishing feature of CMS compared to other postoperative cases in one study [Pollack et al., 1995], but this finding was not replicated [Robertson et al., 2006]. Another theory is that vasospasm and subsequent postoperative ischemia may account for the delayed onset and possible transient nature of mutism [Turgut, 1998; Al-Anazi et al., 2001], however this study has not been supported by radiographic findings. Perhaps, studies employing diffusion tensor imaging will help clarify the type of cellular damage in CMS.

Hydrocephalus has also been hypothesized to be related to CMS. Upon noting that resolution of hydrocephalus coincided with improvement of mutism in many cases, Turgut postulated that CMS is caused by delayed transient ischemia secondary to hydrocephalus and sensitivity of Purkinje cells [Turgut, 2007]. However, other studies have failed to identify hydrocephalus as a specific risk factor and recent reports of long-term sequelae contradict the transient aspect of the argument [Robertson et al., 2006].

It is not known if or how surgical intervention during excision of cerebellar tumors results in the damage that causes CMS. Some investigators believe that more aggressive surgical technique may determine who develops CMS. Di Cataldo et al. [2001] pointed out that CMS had not been reported prior to 1985, and speculated that improvements in imaging and surgical techniques have made neurosurgeons more willing to attempt interventions previously judged impossible. CMS has been shown to occur more often in patients with radical resection than in patients with residual tumors [Van Calenbergh et al., 1995]. The COG prospective study analyzed the occurrence of CMS associated with the performance of surgery by general and pediatric neurosurgeons, and found no difference.

Initially, inferior vermian incisions made during tumor excision were considered possible causes for the development of mutism. A single institution case series found a correlation between CMS and this surgical approach [Dailey et al., 1995]. However, changes in surgical technique that avoid splitting of the vermis have not demonstrated the prevention of CMS [Siffert et al., 2000]. Furthermore, superior and inferior vermian incisions have both been associated with postoperative mutism and it may occur even without damage to median and paramedian structures [Ersahin et al., 2002]. Moreover, the majority of children with midline posterior fossa tumors undergo radical resection through the vermis, and only 25% or fewer develop CMS. The use of surgical retractors has not been studied, although it has been raised as another possible cause [Ozgur et al., 2006]. It is possible that subtle variations in surgical approach may alter the risk of CMS, however, a means of preventing CMS has not been found.

Some investigators have argued that the neurocognitive problems described in patients with CMS may be attributed, at least partly, to the effects of radiation or chemotherapy [Review in Levisohn et al., 2000]. Radiation necrosis is associated with deficits in general intelligence, processing speed, attention and executive functions, visuomotor control, as well as academic achievement, with significant sequelae observed most prominently in younger children [Packer et al., 1989; Palmer et al., 2007; Mabbott et al., 2008]. Methotrexate chemotherapy, most notably intrathecal administration, has also been associated with later neurological and neurocognitive impairments. However, since both radiation and chemotherapy are administered in standard doses and schedules and CMS occurs in a quarter or less of treated patients, it is unlikely that these treatments are the root cause. Moreover, the onset of symptoms is typically days after surgery, before radiation or chemotherapy has been initiated. A recent study showed that patients who received cranial radiation for posterior fossa tumors had demonstrated impairments, but those with postsurgical complications in addition to CRT had the poorest outcomes [Mabbott et al., 2008]. It has been suggested that children who develop postsurgical mutism may be at greater risk for long-term sequelae secondary to damage by radiation and chemotherapy [Glauser and Packer, 1991].

NEUROCOGNITIVE FEATURES

As the survival rate for children with brain tumors has continued to rise, a focus on longer-term effects of the disease and associated treatment has emerged. The known neurocognitive effects and neuropsychological evaluations have become increasingly considered and incorporated into the standard of care for survivors of cancers.

Only relatively recently have there been any studies specifically designed to assess the neurocognitive outcomes of children who have demonstrated postsurgical complications such as CMS, and the majority have been retrospective chart reviews. Nonetheless, several neurocognitive domains have been documented to be disrupted in children who have undergone posterior fossa tumor resection with or without subsequent CMS. The existing literature in children has focused on posterior fossa astrocytoma, medulloblastoma, and more rarely ependymoma. Some research has compared benign and malignant tumors as to control for the effects of radiation and chemotherapy on the longer-term neurocognitive effects.

In a retrospective study, Riva and Giorgi [2000] compared consecutive patients with cerebellar hemispheric astrocytoma to those with cerebellar vermis medulloblastoma within 6 weeks of surgery and prior to any additional treatment (e.g., radiation or chemotherapy). The patients with nonmidline tumors (e.g., astrocytomas) demonstrated a striking lateralizing effect related to verbal (global receptive and expressive language deficits), nonverbal skills (visuospatial fluency), as well as sequential memory (verbal and visuospatial), which has been hypothesized, but not consistently demonstrated in the literature. However, both right and left cerebellar tumor groups exhibited notable executive dysfunction, specifically related to verbal initiation, planning, and set-shifting. Deficits in processing speed were also exhibited.

Six of the eleven medulloblastoma patients exhibited CMS, and those with residual language deficits also demonstrated additional executive function deficits including poor set-shifting and planning. The remainder of the 11 patients were classified as having "behavioral disturbance" without mutism following surgery, however, they also exhibited problems with expressive language and executive functioning, specifically related to verbal initiation and set-shifting.

In a unique case study of CMS, Ozgur et al. [2006] described a 5-year-old with medulloblastoma and associated hydrocephalus. One day postsurgical resection, the patient exhibited cerebellar dysmetria, dysdiadokinesia, and mutism. Although the motor symptoms continued to improve over the next several weeks, the mutism remained. Serendipitously, the patient was exposed to familiar and favorite music and began singing without prompts, but remained mute without the music. However, the patient's speech recovered quickly thereafter. Other symptomatology during that period included decreased initiation, poor regulatory control and attention, impaired language comprehension, and emotional apathy and irritability.

In another study, children with resected medulloblastoma (who routinely receive radiotherapy and chemotherapy after surgery) have also been identified as having poorer long-term cognitive outcome compared to children with astrocytoma (who are usually treated with surgery, alone), specifically with sustained attention, long-term visual memory, and various executive functions including set-shifting or cognitive flexibility and working memory [Ronning et al., 2005]. Both groups demonstrated long-term impairments. Of note, some of these differences may be attributable to radiation effects, as the medulloblastoma group had been treated prior to the assessment period. In this particular study, there was a significant age effect only in the medulloblastoma group such that younger age at diagnosis resulted in poorer outcome.

Aarsen and colleagues studied a group of children with cerebellar pilocytic astrocytoma without radiation or chemotherapy treatment in a retrospective study [2004]. The group exhibited long-term impairments in divided and selective attention, processing speed, visuomotor skills, visual memory, and higher order initiation and set-shifting or flexibility. A lateralizing effect was also reported, such that patients with right cerebellar hemisphere tumor resection exhibited language and verbal memory impairments, while those with left hemisphere resection resulted in impaired visuospatial and nonverbal memory functions. Overall, those with left hemisphere tumors fared worse globally. With regard to developmental effects, Aarsen reported a significant age effect for children diagnosed between the ages of seven and nine and a half compared to those diagnosed prior to seven or later than ten.

Several other studies have demonstrated similar late effects in patients

with CMS, including diminished processing speed, poor verbal initiation and other language deficits, impaired attention, and executive functions (e.g., set-shifting, novel problem solving), as well as memory impairment [Vadeinse and Hornyak, 1997; Aarsen et al., 1995].

It is difficult to ignore the similarities between CMS and the CCAS. CCAS consists of a set of nonmotor deficits that are found in patients suffering from different cerebellar abnormalities and lesions. Schmahmann and Sherman [1998] defined the syndrome after they performed neurological examinations, bedside mental status examinations, neuropsychological studies, and anatomical neuroimaging on 20 patients with diseases confined to the cerebellum. Patients with CCAS demonstrate impairment of executive functions such as planning, set-shifting, verbal fluency, abstract reasoning, and working memory; difficulties with visual-spatial organization and memory; personality change with blunting of affect or disinhibited and inappropriate behavior; and language deficits including agrammatism and dysprosodia. CCAS is attributed to disruption of the cerebellar modulation of neural circuits that link prefrontal, posterior parietal, superior temporal and limbic cortices with the cerebellum. These impairments and the theory behind them may apply to patients with the CMS as well.

Levisohn et al. [2000] evaluated neuropsychological data in 19 children referred for neuropsychological assessment following resection of cerebellar tumors ranging in age from 3 to 14 years. The patients were included if the neurocognitive assessment was completed prior to irradiation therapy, and there was no history of premorbid cognitive dysfunction. Although not a selection criteria, none of the patients received methotrexate chemotherapy. Of the 19 patients included in this study, the majority had medulloblastoma (58%), while astrocytoma (37%) and ependymoma (5%) constituted the remaining patients. Although the disease etiology of the children is unclear, 56% of the 19 children had extensive vermian damage and exhibited CMS as well as additional neuropsychological impairments consistent with those reported in CCAS in adults. Specifically, the authors noted impairments in global intellectual functioning, aspects of executive function, visual-spatial function, expressive language, verbal memory, and modulation of affect during the first 2 years after surgery. They found that lesions of the vermis were highly associated with dysregulation of affect, consistent with the conceptualization of the vermis as the "limbic system" of the cerebellum [Schmahmann, 1991]. While this was a retrospective study, it suggests that the manifestation of CCAS is evident in children and, in the acute setting after posterior fossa surgery, they overlap with those of CMS. It underscores the role of the cerebellum in the distributed neural circuitry subserving higher-order cognitive and behavioral functions.

The key components of CCAS—disturbances of executive function, visuospatial skills, nonmotor language, and affect regulation—have all been described in patients with CMS. The major distinction between CCAS and CMS appear to relate to the chronicity of the symptoms, with the latter seemingly more transient. However, patients who have been described as having CCAS have undergone thorough neuropsychological evaluation, allowing for the identification of more specific neurocognitive deficits, whereas this has rarely been studied in children with CMS, as much attention has been paid to the transient loss of speech rather than the potential cognitive sequelae [Sadeh and Cohen, 2001].

Mutism appears to be a key feature of the initial presentation of many children with CCAS, particularly if the children have damage to the cerebellar vermis. More neuropsychological and functional neuroimaging studies of well characterized groups of children and adults with CCAS and CMS may shed light on the nature of these syndromes and the extent to which their clinical overlap is anatomically based.

Criteria for CCAS in children are not yet defined. When Levisohn et al. described CCAS in their pediatric population, they included patients with some, but not all of the characteristic set of behaviors [Levisohn et al., 2000]. Reports of the neuropsychological and behavioral consequences of CMS demonstrate variations in the affected cognitive domains. The extent to which there is overlap between patients with CMS and features of CCAS is not yet known. Mutism appears to be a key feature of the initial presentation of many children with CCAS, particularly if the children have damage to the cerebellar vermis. More neuropsychological and functional neuroimaging studies of well characterized groups of children and adults with CCAS and CMS may shed light on the nature of these syndromes and the extent to which their clinical overlap is anatomically based. Executive functional impairment, a central feature of CCAS in adults, has been poorly characterized in children with CMS and needs further study.

WHAT CMS TEACHES US ABOUT CEREBELLAR FUNCTION

In recent years, the role of the cerebellum in higher cognitive functions has become increasingly clear. There is a complex circuitry between the cerebellum and cerebral cortex, and diaschisis secondary to disruption of this circuitry has been proposed to be the likely etiology of neurocognitive, psychological, and behavioral alterations observed in CMS. Once considered solely responsible for coordination of purposeful motor movement, the contribution of the cerebellum to higher-order cognitive function such as language, cognitive and behavioral regulatory control, and executive functions (including initiation, novel problem-solving, working memory, and cognitive flexibility) have been demonstrated [Review in Riva and Giorgi, 2000]. This understanding has evolved over the past 20 years and has been supported by case reports and increasingly more sophisticated neuroimaging studies [Leiner et al., 1986, Middleton and Strick, 1994, Steinlin, 2007, Timmann and Daum, 2007]. Functional MRI and PET studies have shown activation of the cerebellum during nonmotor tasks, including executive [Bellebaum and Daum, 2007], expressive language [Petersen et al., 1988], and verbal memory tasks [Andreasen et al., 1995]. The role of the cerebellum in emotional behavior has been demon-

strated in primates with cerebellar lesions. Other evidence that the cerebellum plays a role in higher-order behaviors comes from imaging studies of children with neuropsychiatric and genetic disorders such as Attention Defict/Hyperactivity Disorder (ADHD), autism, developmental dyslexia, Fragile X, Down syndrome, and schizophrenia. [Chang et al., 1998; Mostofsky et al., 1998; Giedd et al., 2001; Nicolson et al., 2001; Pinter et al., 2001; Eckert et al., 2003; Cornish et al., 2005; Stoodley et al., 2006; Zang et al., 2007].

Initially, case reports of CMS focused on the motor speech aspect. At a time when neuroscience focused on functional domains and the cerebellum was primarily understood to coordinate movements, researchers proposed that a loss of coordination of orofacial movements is mainly responsible for the development of mutism. This theory was supported by reports that the time course of development and recovery from mutism follows the loss and regain of simple orofacial movements as well as coordination of oral and pharyngeal phases of swallowing [Dailey et al., 1995; Van Mourik et al., 1997]. However, normal oral movements and swallowing in some patients with CMS indicate that the problem is not purely motor [Dietze and Mickle, 1990]. It has also been suggested that CMS may represent an extreme form of dysarthria [Van Calenbergh et al., 1995]. Dysarthria due to cerebellar infarction has been described for all vascular territories of the cerebellum, with the superior cerebellar artery being most often affected and the rostral paravermal area of the anterior lobe the most frequent lesion site. FMRI data of healthy volunteers show activation of this area during articulatory movements of the tongue and orofacial muscles [Urban et al., 2003]. Recently, a more complex role in speech production has been proposed. Nonmotor pathways of speech subserve the internal generation of words, word choice, speech rehearsal, and vocal intonations used in speech production, and can be localized to the posterior lateral hemispheres of the cerebellum [Tohgi et al., 1993]. The findings in CMS add to the growing body of evidence that the cerebellum is involved in both coordination of orofacial movements and the cognitive component of speech generation [Ozgur et al., 2006].

In cases of cerebellar dysfunction, it is often difficult to differentiate the contribution of the cerebellum from other structures and connections in the cerebellar-pons-cerebrum circuit. Many cases of cerebellar abnormalities involve not only cerebellar damage, but also cerebral cortical structural or functional abnormalities. However, the development of cerebellar tumors usually occurs without cerebral damage, either preor postoperatively. MRI studies have shown very few cases of damage to the cerebrum in patients with postoperative CMS. Thus, CMS enables us to examine outcomes in patients without cerebral damage and further supports the importance of the posterior fossa in both motor coordination and higher-order cognitive function.

Levisohn et al. [2000] found that patients with CMS including affective changes also demonstrated cognitive impairment, but patients with cognitive changes did not necessarily show CMS and affect disturbance. This finding is consistent with the hypothesis that affect regulation is principally a function of the vermis and fastigial nucleus, but both the vermis and the cerebellar hemispheres are involved in executive, linguistic, and visual-spatial functions [Schmahmann, 1991; Tavano et al., 2007]. At this time, studies have not clearly indicated how many patients with mutism also have affective changes, although the two are often described together in patients with CMS. Demonstrating that mutism rarely occurs without affective changes would further support a functional neuroanatomic overlap between these two features.

Most cases of postoperative CMS have occurred in the pediatric age group [Ildan et al., 2002]. Some studies have found younger age at diagnosis to be associated with poorer outcomes [Packer et al., 1989; Mulhern et al., 2001; Ronning et al., 2005], some studies have found young age to be protective [Levisohn et al., 2000], and others have found no association [Mabbott et al., 2008]. These differences may be due to patient population differences. For instance, in Levisohn's study, the majority of younger children nonmedulloblastoma tumors and were therefore at lower risk for CMS. In a review of pediatric studies supporting the role of the cerebellum in cognitive processes, Steinlin [2007] concludes that earlier damage leads to more pronounced problems. He hypothesizes that the most important function of the cerebellum is learning, either during development or later on during a rehabilitation process. The reason why mutism occurs in children and not typically adults with CCAS may be related to the higher incidence of damage to the cerebellar vermis and nearby nuclei in children, as posterior fossa tumors including medulloblastoma are much more common in children than adults. Mutism may also be related to developmental factors including the absence of well-myelinated pathways for initiation of speech and other behaviors. Although lack of myelination may make them prone to surgical injury from either direct insult or retraction, it may also make them more capable in recovery and redirection [Ozgur et al., 2006].

CONCLUSION

Tumors of the posterior fossa account for half of all brain tumors in children [Packer et al., 2008]. As the prognosis for survival is improving as a result of advances in treatment, clinicians and researchers are paying greater attention to the long-term neurocognitive and psychological sequelae associated with the tumor and its treatment. Earlier studies of outcomes for patients with brain tumors focused on survivorship and general intellectual function. Improved survivorship and a growing collaboration between neurology, neurosurgery, neuroradiology, and neuropsychology have led to more research on treatment-related deficits in these children. Over the past 25 years, more than 300 cases of mutism and associated behavioral and personality changes have been reported after the removal of posterior fossa tumors. Neuroradiographic studies have failed to demonstrate consistent preoperative or immediate postoperative findings that predict who will develop CMS. Although the syndrome is considered a postoperative complication, a specific change in surgical technique has not been proven. Given the significant increase in survivorship of patients with more aggressive resection and the lack of evidence for a specific mechanism of injury, there are currently no recommendations for changing surgical technique. Future research needs to address the seeming vulnerability to CMS in some patients. Perhaps functional MRI could shed light on whether differences in brain organization put certain individuals at risk for CMS. Such knowledge could also help guide rehabilitation and counseling, as long-term prognosis is currently poor. ■

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