Bilateral supplementary motor area syndrome causing akinetic mutism following parasagittal meningioma resection

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Abstract

The supplementary motor area (SMA-proper) is important for the programming and execution of motor, speech, and other elaborative functions. Unilateral SMA syndrome is well described. We present two patients who underwent resection of a large parasagittal meningioma in proximity to the SMA-proper in both hemispheres. Following surgery, these patients developed akinetic mutism; the maximal clinical deficit was not immediately evident, but manifested at 48 hours and 1 week respectively. Both patients showed complete recovery of neurological function but the process was slow. Initial return to near normal function was noted at approximately 3 months with a specific pattern; return of strength was first noted in the upper extremities followed by the lower extremities and speech and cognitive function was the last to recover. The unique occurrence of akinetic mutism secondary to bilateral SMA involvement by parasagittal meningiomas of the posterior frontal region is rare. We discuss the clinical and neuropsychological outcomes in these patients along with an analysis of the possible underlying neurophysiological mechanisms of this unique phenomenon.

Keywords: Akinetic mutism, bilateral SMA syndrome, supplementary motor area, parasagittal meningioma

Introduction

The supplementary motor area (SMA) was originally defined by Penfield and Welch in 1951 as a single cortical field anterior to the leg representation of the primary motor cortex (PMC) along the medial aspect of the cerebral hemisphere down to the cingulate sulcus [1-4]. The SMA-proper is limited to cortex within five centimeters anterior to the precentral sulcus corresponding to Brodmann’s area 6 [1-5]. It is superior to the premotor cortex that occupies the middle and inferior frontal gyri; thus the lateral extent of the SMA-proper is the superior frontal sulcus. The SMA-proper plans, initiates, and coordinates complex bimanual actions and motor sequencing, and helps maintain an erect posture. It is involved in conditional behavior learning and the production of speech [1,3,6-17]. Recent studies suggest an even wider area, the supplementary motor complex, which includes the SMA, the pre-SMA, and supplementary eye fields, serves as a crucial link between cognitive function and elaborative action [1,10,11,18-20]. The SMA-proper also collaborates closely with adjacent cortical areas; for example, tight coupling and co-activation of the SMA-proper and the PMC in visually guided movements is seen [4,13,21]. The pre-SMA may be the area involved in the executive and cognitive aspects of these complex functions [3,6,9,12,14,16,19,22].

The SMA syndrome is a well-described neurological condition characterized by a contralateral motor neglect that manifests as hemiplegia, and expressive aphasia that manifests as mutism. An ideomotor apraxia is observed; patients are unable to execute learned motor acts. The SMA syndrome is due to iatrogenic or pathogenic SMA cortical injury. Unilateral SMA syndrome is reported and well recognized, particularly by surgeons operating on intra-axial neoplasms, such as gliomas, in the SMA [23-33]. By contrast, bilateral SMA involvement, or syndrome, is not as commonly seen, and its manifestations and pattern of recovery are not well described. We present two patients, each with a large parasagittal meningioma that spanned both hemispheres compressing the SMA on both sides, who developed akinetic mutism following an uncomplicated resection of the tumors. The neuropsychological profile in these patients is discussed.
as it compares to patients with classical unilateral SMA syndrome, along with an analysis of possible underlying neurophysiological mechanisms.

Case presentation
Case 1
This 42-year-old right-handed Caucasian woman presented with a two-month history of progressively worsening headaches. She had undergone resection of a large parafalcine tumor about 11 years previously, and the pathology was reported as a solitary fibrous tumor. Her neurological examination was normal except for 4+/5 weakness in the left upper extremity. Cranial magnetic resonance imaging (MRI) demonstrated a 7x6x6.5 cm homogeneously contrast-enhancing, lobulated parasagittal mass that straddled the superior sagittal sinus (SSS) and falx and extended bilaterally, compressing the posterior aspect of the frontal lobes in the region of the SMA (Figures 1A and 1B). Moderate peri-tumoral vasogenic edema, along with dural enhancement and calvarial bone involvement, was noted. A pre-operative angiogram showed no flow in the SSS anterior to the lesion (Figure 2). She underwent a bifrontal craniectomy, with gross total resection of the tumor, along with removal of involved bone and dura (Figure 3A). The SSS was ligated and removed where it was invaded and occluded by tumor anterior to the PMC, but in the region of the SMA. Tumor pathology was a World Health Organization (WHO) Grade II meningioma; although the Ki-67 labeling index was <1%, glial fibrillary acidic protein staining indicated invasion of adjacent cortex. The dura and calvarial defects were reconstructed with a synthetic dura substitute and titanium mesh respectively.

Immediately following surgery, she opened her eyes spontaneously and was noted to have 4/5 strength of the upper extremities with 2/5 strength in the lower extremities. Cranial MRI, approximately two hours after surgery, showed normal post-operative changes with mild vasogenic edema without evidence of infarction or a hematoma (Figure 3B). An electroencephalogram revealed a background of irregular polymorphic delta activity but no epileptiform discharges or electrographic seizures were noted. Over the next two days, the patient’s neurologic exam deteriorated further, and she became completely aphasic, aphonoc and quadriplegic. However, she remained awake and alert. Her eyes were open and she would regard, track, and grimace to pain. Her early post-operative course was complicated by deep vein thrombosis and subsegmental pulmonary embolus for which an inferior vena cava filter was placed. Persistent respiratory failure necessitated tracheostomy placement, and a percutaneous gastrostomy tube was placed for enteral nutrition.

She remained awake and alert, but completely aphasic, aphonoc, and quadriplegic until the 16th postoperative day, when her neurological examination began to improve. The recovery of function was initially noted in the upper extremities, while the lower extremities demonstrated 0/5 strength. She was discharged on post-operative day 29 to a skilled nursing facility, where she made excellent progress with physical, occupational, and speech therapy. Three months after surgery, she had complete return of all motor function in the upper extremities.

Figure 1. Axial (A) and coronal (B) post gadolinium enhancement T1 weighted MRI images shows a midline parasagittal tumor with bihemispheric extension and compression of both supplementary motor areas and the primary motor cortex (arrow) on the right side.
and lower extremities but had a persistent motor apraxia; her speech had improved but she had some persistent dysphasia. About six months after surgery, the patient had regained all gross motor and sensory function. However, neuropsychological testing revealed selective deficits in praxis, psychomotor speed, and problem solving. Speech production was impaired and fluency was slow. Difficulty with transitive and intransitive gestures to command, bimanual sequencing, 3-D construction, and copying overlapping elements was noted. At one year from surgery, the patient showed improvement in speech fluency, psychomotor speed, and intransitive gestures for each hand, but transitive gestures, bimanual actions, finger dexterity and complex constructions remained impaired. At two years after surgery, she was noted to have normal neurological function with complete recovery of all motor, speech and neuropsychological deficits and a follow-up MRI showed no evidence of recurrent tumor (Figures 4A and 4B).

Case 2
This 53-year-old right-handed Caucasian woman presented with a seizure involving the left upper and lower extremity. Her neurological examination was normal, except for a positive Babinski sign on the left and hyperreflexia in both lower extremities. A cranial MRI demonstrated a 6.5x6.5x4.6 cm homogenously contrast-enhancing, parasagittal mass crossing the midline with surrounding vasogenic edema. Adjacent dural enhancement and destruction of the inner table of the calvarium and extension into the diploic space was noted (Figures 5A and 5B). A pre-operative MR venogram showed occlusion of the SSS at the midpoint (Figure 6). She underwent a bifrontal craniectomy with gross total resection of the tumor along with removal of involved bone and dura (Figures 7A and 7B). The SSS was ligated and removed where it was invaded and occluded by tumor in the region of the SMA. Closure with a synthetic dura substitute and skull defect with a titanium mesh followed. The tumor pathology was consistent with a WHO Grade I meningioma with a Ki-67 labeling index 3-5% in most areas and 10% in focal microscopic areas.

Following surgery, she had a right lower extremity focal motor seizure and intravenous phenytoin was added to the levetiracetam she was receiving. Cranial CT showed postsurgical changes with no acute pathology. Her eyes were open, but she was not tracking, and she withdrew both lower extremities and flexed both upper extremities to painful stimulus.
One week after surgery, she was extubated uneventfully, but noted to be aphasic and had 0/5 strength in all four extremities. At postoperative day 15, she started to move her toes to command and her extremity strength started to improve initially in the upper extremities and subsequently in the lower extremities; the aphasia persisted.

At three months after surgery, she had regained near normal strength in both upper and lower extremities. She was able to ambulate with assistance, but had a gait ataxia. Her speech had improved, but she had subtle cognitive problems. At six months from surgery, her neurological examination was normal except for subtle cognitive problems. At two years from surgery her cognitive, speech and motor function had returned to normal and a follow-up MRI (Figures 8A and 8B) at that time showed no recurrent tumor.

**Discussion**

The SMA-proper is agranular (it lacks layer IV, the granular layer)
and poorly laminated, without well-defined cortical areas. The SMA-proper, like the PMC, is somatotopically organized from rostral to caudal and has a high density of subcortical efferent projecting axons. It has connections to the ipsilateral premotor, primary motor, and orbitofrontal cortex, and the striatum, ventrolateral thalamus, and corticospinal tracts \[13,18,34-36\]. The dominant SMA-proper is also connected to the inferior frontal gyrus by the frontal aslant tract and plays a role in the production of speech \[13,18,34-36\]. On the afferent side, the SMA-proper receives input from the globus pallidus, thalamus, cerebellar dentate nucleus, and the primary sensory cortex \[1,4,15-17,20,33-35,37-44\].

The pre-SMA has similar afferent input as the SMA-proper. The efferent connections of the pre-SMA are to the prefrontal cortex, insula, cingulate gyrus, superior frontal gyrus, caudate, anterior thalamus, and anterior putamen \[1,21,34,35,37,39-43\]. Functional imaging studies demonstrate a tight coupling between SMA-proper activation and the control and generation of movement, while pre-SMA activation is more tightly coupled to cognitive, non-motor tasks \[1,21,45\]. In summary, these connections allow the SMA-proper, and its adjacent functionally related areas (the supplementary motor complex), to serve as a crucial link in the intent, specification, and elaboration of actions \[10\] (Figure 9).

Nearly 30% of diffuse low grade gliomas and 10% of malignant gliomas may involve the SMA-proper \[46\]. However, given its important role in the elaboration of motor function, and speech on the dominant side, the SMA-proper was historically avoided during surgical resection of lesions in the frontal cortex. Laplante provided a critical breakthrough when he discovered the transient nature of these neurologic deficits presenting evidence that within one month of surgery, the neurological deficits, hemiparesis and mutism, had resolved \[22\]. Surgical forays into the SMA-proper to resect tumors followed and this pattern of recovery duplicated.

The SMA syndrome is seen in 40-50% of patients following

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Figure 8. Follow-up axial post gadolinium T1 weighted (A) and FLAIR (B) MRI 2 years from surgery shows no recurrent tumor.

Figure 9. Line drawing depicting the connections (arrows) of the supplementary motor area (SMA) and pre-SMA. VA: Ventral anterior thalamic nucleus, VL: Ventral lateral thalamic nucleus, DM: Dorsomedial thalamic nucleus.

resection of tumors from the SMA-proper; most patients predictably recover to their pre-surgical function, but in 10-20% the deficits may be permanent [23,24,26-33,46]. Unilateral SMA syndrome is a severe impairment of volitional movements and a hemineglect and apraxia involving the contralateral side that manifests as hemiparesis. Dominant hemisphere SMA-proper involvement also results in aphasia or mutism [30,33]. While patients are not able to follow motor commands, they have been able to produce reflex movements to external stimuli. The syndrome usually follows infarction or surgical entry into the SMA-proper, and characteristically manifests either immediately following surgery to resect a tumor from the SMA-proper, or cortical injury to the SMA-proper, or a few days later. Most characteristic is a pattern of progressive recovery of function that usually begins within a week after surgery and results in return of function to pre-surgical or pre-morbid levels. Motor improvement usually proceeds distal to proximal, and speech returns starting with sound mimicking. Mutism is better described with involvement of dominant SMA-proper, but may be seen with non-dominant hemisphere SMA syndrome, as well. The clinical diagnosis is clinched with resolution of the characteristic deficits.

The akinetic mutism observed with bilateral SMA syndrome can be alarming. These two patients demonstrated bilateral motor apraxia that progressed to quadriplegia along with akinetic mutism, and the recovery was not as rapid as seen with unilateral SMA syndrome. During this phase, even reflex motor responses were absent. Bilateral involvement or injury to the SMA-proper has been previously reported and, there are similarities to the cases described here. One report describes a bilateral, distal anterior cerebral artery territory stroke resulting in isolated ischemic lesions in both SMA-proper with resultant spastic paraplegia and hypophonia. A month later, the patient was able to walk with crutches, and at 5 months, he had only minimal weakness with an apraxic gait. At 14 months, he was found to have only mild residual weakness on the right, but
maintained significant gait apraxia [24]. Another case is reported of paraparesis, with no mention of speech deficits, following resection of a parasagittal meningioma with bilateral extension. The surgery involved ligation of the middle third of the SSS. Postoperative imaging demonstrated bifrontal white matter edema. With intensive neurorehabilitation, the patient improved in motor function at 6 weeks and had a near complete recovery by one year [29].

It is generally accepted that when tumors or vascular malformations affect the SMA-proper, the contralateral SMA-proper assumes some of its function [32]. The transient nature of motor and verbal deficits seen in unilateral SMA syndrome is postulated to be due to this redundancy, and also due to the bilateral connectivity of the SMA-proper, with subsequent neuroplasticity allowing for redirection of complex tasks [47,48]. Duffau, et al., postulate that short-term recovery of gross motor function is based on unmasking of parallel pathways and long-term, steady improvement based on plasticity [25]. With bilateral SMA-proper involvement, recovery of function appears to be slower and may be due to a different mechanism.

In both cases described here, the tumors were extra-axial and the SSS was occluded. Although there are reports of transient hemiparesis following SSS ligation in the resection of parasagittal meningiomas, it is generally considered safe to resect a portion of the SSS if it is occluded by tumor, as done in these cases. However at times, the onset of neurological deficits may be delayed. In one case report by Oh, et al., a patient is described as having a stable neurologic exam immediately post-operatively, but in the following six hours, the exam degraded to a left sided hemiparesis and stupor. Only moderate edema was noted on postoperative MRI and the patient recovered completely four days later [49]. Sindou and Alvernia in 2006 and DiMeco in 2004 describe cohorts of patients having undergone SSS ligation following meningioma resection [50,51]. While the location of the meningioma and the portion of SSS ligated vary, there are reports of patients that had deficits post-operatively that improved with time [50].

The most likely etiology of transient deficits following SSS ligation is venous hypertension and edema, but these are readily detected on postoperative CT perfusion or MRI studies. Although both patients in this report had a delay in the onset of their neurological deficits, there was radiographic occlusion of the SSS documented prior to surgery and there was no overt cortical venous stasis or infarct on the postoperative MRI. The literature also does not suggest that SMA syndrome is a sequela of ligation of the middle third of the SSS [23-32]. Post-operative edema commonly follows resection of large intra-axial and extra-axial cranial neoplasms, and may also be a cause of cortical malfunction. The dysfunction may be related to tumor invasion into adjacent cortical areas or neuronal stretch injury associated with re-expansion of the brain following resection of a large compressive neoplasm. Transient ischemia associated with post-operative vasospasm is another possibility, but no perfusion deficits were noted on post-operative MRI. Post-operative epileptic activity within the SMA-proper may also cause a similar clinical picture, although that was not observed in these cases. Hence, we can surmise that the neurological deficit and subsequent recovery could have been a result of compromise of cortical function in the SMA-proper bilaterally.

The neuropsychological evaluation of postoperative acute SMA syndromes should affirm that cognition and motor control are grossly intact; attention, perception, communicative language, writing, drawing, anterograde memory, comportment, and reasoning are expected to be spared. Unilateral SMA syndrome is characterized by transient problems with complex motor movement and speech production. Bilateral SMA syndrome may be characterized by more subtle problems with initiation, coordination and cognitive efficiency as well as by more chronic apraxia. Deficits are assessed by fractionation of function from basic skill to complex skill. This approach helps with tracking recovery and with guiding neurorehabilitation. Both patients described here had resolution of their neurological findings while neuropsychological testing revealed persistent sensorimotor and ideomotor apraxia [24,52]. The profile was distinct from what one would expect in the case of compromise of corpuscallosum function [8,27,30,43,47,53-55].

With unilateral SMA syndrome, complete recovery approximately one to two weeks after onset is expected. The pattern of recovery of in these cases differed in some aspects. Firstly, it was more gradual in onset and the recovery spanned weeks to months necessitating careful supportive care. Motor recovery preceded return of speech and cognitive deficits, and improved from distal to proximal in the upper extremities before the lower extremities [24,29,30,33,52]. It was also characterized by a chronicity of apraxic deficits. The first patient described in this report continued to demonstrate significant bimanual incoordination and impaired transitive gestures to command almost a year after resection. Neuropsychological testing was hence an essential part of the care and treatment of these patients and through longitudinal testing, subtle or persistent neurobehavioral deficits were monitored and used to guide neurorehabilitation efforts in the recovery phase.

Conclusion
The SMA syndrome is a well-defined clinical entity that is seen following resection of lesions in the region of the SMA-proper. Neurological deficits generally involve contralateral motor function and expressive speech when the dominant SMA is involved. Akinetic mutism secondary to bilateral SMA-proper involvement by a parasagittal meningioma is less commonly reported. The onset of neurological deficits was delayed and the recovery prolonged. Recovery of motor function in the upper extremities before the lower extremities and from distal to proximal was noted and preceded the recovery of speech and cognitive function. The syndrome described here can occur despite a meticulous surgical resection with minimal
resection of adjacent cortical tissue and preservation of major arterial vessels. However, postoperative imaging to rule out hemorrhage or infarction is essential and the diagnosis is clinched with a pattern of functional recovery to premorbid levels. Neuropsychological testing is helpful and may detect a residual apraxia or speech impediment that may guide neuro-rehabilitation efforts.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

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