**ANOMALOUS DEVELOPMENT OF BRAIN STRUCTURE AND FUNCTION IN SPINA BIFIDA MYELOMENINGOCELE**

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Spina bifida myelomeningocele (SBM) is a specific type of neural tube defect whereby the open neural tube at the level of the spinal cord alters brain development during early stages of gestation. Some structural anomalies are virtually unique to individuals with SBM, including a complex pattern of cerebellar dysplasia known as the Chiari II malformation. Other structural anomalies are not necessarily unique to SBM, including altered development of the corpus callosum and posterior fossa. Within SBM, tremendous heterogeneity is reflected in the degree to which brain structures are atypical in qualitative appearance and quantitative measures of morphometry. Hallmark structural features of SBM include overall reductions in posterior fossa and cerebellum size and volume. Studies of the corpus callosum have shown complex patterns of agenesis or hypoplasia along its rostral-caudal axis, with rostrum and splenium regions particularly susceptible to agenesis. Studies of cortical regions have demonstrated complex patterns of thickening, thinning, and gyration. Diffusion tensor imaging studies have reported compromised integrity of some specific white matter pathways. Given equally complex ocular motor, motor, and cognitive phenotypes consisting of relative strengths and weaknesses that seem to align with altered structural development, studies of SBM provide new insights to our current understanding of brain structure–function associations.

**OBSERVATION OF NEUROIMAGING FINDINGS IN SBM**

Common structural characteristics associated with SBM include anomalous development of the skull, as well as infratentorial regions of the brain [McLone and Dias, 2003]. Chiari II malformation (CII) is a complex congenital anomaly that involves the midbrain, hindbrain (i.e.,pons, medulla, and cerebellum) and cervical spinal cord [Harding and Copp, 2002; Barkovich, 2005], which occurs universally and exclusively in SBM [Wagner et al., 2002]. Prominent features of CII include a significantly smaller posterior fossa with its contents crowded and distorted in appearance [Barkovich, 2005]. Additional features of SBM can include tectal beaking, hydrocephalus, and corpus callosum hypoplasia and dysgenesis, but these features are variable. Although less studied, an enlarged massa intermedia and gyral malformations of the neocortex also occur commonly in SBM with CII.

The main features of CII are based on qualitative and quantitative descriptions of gross anomalies (Table 1), particularly midline brain structures [McLone and Dias, 2003]. The mesencephalic tectum is often distorted and stretched posteriorly and inferiorly (see Fig. 1), which is frequently described on magnetic resonance imaging (MRI) scans as “beaking” of the tectum. Tectal beaking is reported to occur in 75% of CII cases, being particularly prominent in older patients with an extensive myelomeningocele [Fletcher et al., 2005]. Typically in CII, the brainstem is stretched down to the level of the foramen magnum or cervical spine with narrowing in its anteri-
or–posterior diameter. A cervico-medullary kink may be seen at the junction between the cervical spinal cord and the medulla oblongata [Barkovich, 2005], which may lead to symptoms of spinal cord compression [Oaks and Gaskill, 1992]. Although the inferior vermis frequently herniates down to the upper cervical vertebrae (C), at C2 or C4 level, the superior part of the cerebellar vermis herniates upward (Fig. 1). As described by Barkovich [2005] and shown in Figure 2, the cerebellum wraps around the brainstem. In some cases, low insertion of the tentorium cerebelli, cerebellar dysplasia, agenesis, or hypoplasia of the lateral cerebellar hemispheres also occurs [Gilbert et al., 1986; Harding and Copp, 2002; Barkovich, 2005].

Morphology of the corpus callosum (CC) is also compromised during early embryogenesis in SBM [Barkovich, 2005] as the CC programmed pattern of development usually occurs in utero between 7 and 20 weeks of gestation [Barkovich and Norman, 1988]. Complex patterns of CC morphodology occur along its rostro-caudal axis in SBM [Hannay et al., 2009]. Although partial agenesis or dysgenesis and hypoplasia (e.g., underdevelopment) are descriptively termed frequently to communicate type of dysmorphology, the genu, body, splenium, and rostrum are subdivisions of the CC used to communicate where the dysmorphology has occurred [Fletcher et al., 2005; Miller et al., 2008]. An association has been reported between spatial location of CC agenesis and level of the vertebral column where the myelomeningocele occurs (e.g., thoracic versus lumbar/sacral), with thoracic lesions being twice as likely to have agenesis of the splenium as lumbar/sacral level lesions [Hannay et al., 2009]. Thin regions of the CC are generally thought to develop secondary to increased intracranial pressure and hydrocephalus, which develop in 80–90% of children born with SBM [Reigel and Rotenstein, 1994].

### Theories and Mechanisms of Chiari Type II Malformation

Over the years, several theories have been proposed to explain CII. Although no single theory fully accounts for all features of CII [Stevenson, 2004; Tubbs et al., 2008], the currently most widely accepted theory is the "unified theory" [McLone and Knepper, 1989]. According to this theory, cerebrospinal fluid (CSF) leaks through the spinal defect into the intracranial environment. Failure of neural tube closure hinders normal distension of the embryonic ventricular system through the pressure generated from CSF buildup during the temporary period of spinal neurocele occlusion [Desmond, 1982]. Lack of ventricular distension in utero limits the normal growth of the bony elements of the posterior fossa, which significantly reduces posterior fossa size [McLone and Knepper, 1989; McLone and Dasp, 2003]. The contents of the posterior fossa, which proliferate rapidly later [Griffiths et al., 2004], are constrained by a smaller than normal posterior fossa, thereby leading the cerebellum to compression and subsequent volumetric reduction as well as displacement and herniation along its vertical and anterior–posterior axes.

In light of the unified theory, several testable hypotheses to prevent CII from developing have emerged. The basic rationale is that preventing CII will also prevent downstream consequences of CII [Walsh et al., 2001]. Specifically, one might predict that fetal surgical techniques designed to repair the spinal defect in utero would stop CSF leakage through the meningocele, thereby preserving normal distension of the ventricular system, and thus facilitating normal bone growth [see Bowman and McLone, 2010]. Reports of reduced or prenatal resolution of hindbrain herniation following surgical repair of spinal meningocele in both animal model systems [Meuli et al., 1995] and human patients [Adzick et al., 1998; Bruner et al., 1999; Sutton et al., 1999; Tulipan et al., 1999] are consistent with the unified theory. Additionally, infants with SBM who had fetal surgery to close their spinal defect have decreased symptoms and signs of brainstem compression [Danzer et al., 2008]. Currently, an NIH-funded multicenter study is conducting a prospective randomized clinical trial (e.g., Management of Myelomeningocele Study) to compare efficacy of prenatal fetal surgery with standard postnatal repair on improving neurological outcome and reducing anomalous brain development in SBM [Mitchell et al., 2004; Sutton and Adzick, 2004; Bowman et al., 2009; Bowman and McLone, 2010].

Additional theories proposed to explain CII that have not been widely supported include: hindbrain dysgenesis theory, which postulated that the hind-
brain was underdeveloped in SBM; the traction theory in which downward traction of the lower spinal cord was thought to pull down the hindbrain into the spinal canal; the overgrowth theory, which suggested there is overgrowth of the neural tissue prior to closure of the neural tube; and the hydrodynamic theory in which there is downward herniation of the hindbrain caused by the raised intracranial pressure from the hydrocephalus [Gardner et al., 1969]. In young neo-

nates, significant reduction in cerebellar weight was found in 100 children with SBM, who died within 4 weeks of birth, in comparison with cerebellar weight of 60 children with normal ver-

nis who died from other causes [Var-

riend and Emery, 1973]. Subsequent degeneration of the cerebellum in CII, also referred to as “vanishing cerebel-

um,” in CII has also been reported (e.g., in Sener’s [1995] study of four children, age 1 month to 4.5 years, using magnetic resonance imaging (MRI) of the brain). Microscopic stud-

ies have described reduced cell numbers and DNA content, particularly in the internal granular layer of the inferior vermis, in 100 children with SBM compared with 120 controls [Emery and Gladson, 1975]. More recently, mi-

croscopy analyses of herniated cerebellar tissue have documented granule and Purkinje cell loss, reduction and gliosis of the folia, and myelin depletion [Har-

ding and Copp, 2002].

Distance measurements, planimetry (e.g., area measurements), and bio-

metric (e.g., shape) analyses of the post-

erior fossa and its contents have been performed in MRI studies of individu-

als with SBM to quantify abnormalities, document variability, and predict func-

tion or prognosis. In SBM, the longest transverse and longitudinal distances across the midsagittal vermis indicated expansion, not reduction, relative to age-matched controls [Salman et al., 2006a]. In the same study, mean area measurements of the midsagittal vermis (anterior, posterior, and inferior subdivisions) were significantly increased by 25% in SBM compared to normal controls despite a 9% reduction in posterior fossa area measurements in SBM [Salman et al., 2006a]. Using shape analyses, Tsai et al. [2002] quantitatively documented the tremendous variability across individuals with SBM in the degree to which the hindbrain is mal-

formed. According to their findings, shape changes in bone and vermian descent co-occur in a relational fashion. However, herniation of the cervico-

medullary junction appears to be inde-

pendent of vermian herniation, thereby suggesting different etiologies for herniation of the vermis and herniation of the cervico-medullary junction.

Early volumetric studies of the cerebellum in a group of individuals with SBM used noninvasive MRI methods to quantitatively assess group differences between 52 children with SBM and 16 age-matched controls [Dennis et al., 2004]. Although this study found significantly reduced cerebellar volumes in the SBM group, it also described a significant effect of lesion level on cerebellar gray matter (GM) and white matter (WM) volumes. Consistent with neurological outcomes, where individuals with lower level spi-

nal lesions are less impaired than those with thoracic level lesions, higher spinal lesion levels exhibited greater reductions in cerebellar volumes of GM and WM (~37%) than those with lower level lesions (~22%) [Dennis et al., 2004]. Another study of children with SBM [Fletcher et al., 2005] reported reduced cerebrum and cerebellar volumes in children with upper (n = 25) in comparison with lower (n = 61) spinal lesion levels. Together, these studies demonstrate that upper level spinal lesions in SBM are a marker of more severe brain dysmorphism and are associated with poorer cognitive and behavioral outcomes [Dennis et al., 2004; Fletcher et al., 2005].

A recent volumetric MRI study used a simple approach for parcelling the cerebellum into meaningful subu-

nits: the corpus medullare, the anterior lobe, and the posterior–superior and posterior–inferior subdivisions [Juranek et al., in press]. Despite the overall reduction in cerebellar volume in the SBM group, the absolute volume of the anterior lobe was signifi-

antly increased relative to a typically developing comparison group. Although the absolute volume of the corpus medullare was significantly reduced in the SBM group, the relative volume of the corpus medullare was not signifi-

antly different from the typically developing group when corrected for total cerebellar volume. As shown in Figure 3, the smaller cerebellum observed in individuals with SBM is not simply, linearly reduced equally across all regions, but rather disproportionately enlarged in the anterior lobe, reduced in the poste-

rior–inferior subdivision, and not signifi-

antly different in the corpus medullare or the posterior–superior subdivision.

The functional significance of regionally specific patterns of volumet-
ric enlargement and reduction in cerebellar subdivisions remains to be established. Although the anterior lobe is generally associated with motor function, it is not yet clear whether a larger anterior lobe confers advantages or disadvantages in the motor function domain. Individuals with SBM demonstrate a wide range of deficits in motor skills requiring strength or speed [Hetherington and Dennis, 1999] or dynamic regulatory control [Sandler et al., 1993; Jewell et al., 2009]. In contrast, they perform pretty well on motor skills requiring learning and adaptation [Colvin et al., 2003; Edelstein et al., 2004; Dennis et al., 2006a]. Thus, ongoing studies investigating these types of brain structure-function associations are ideally suited to provide new knowledge and insight for continued progress in hypothesis-driven research.

Consequences of Chiari Type II Malformation on Hindbrain Motor and Visceral Functions

Intrinsic brainstem abnormalities and pressure on the brainstem from a crowded posterior fossa and hydrocephalus give rise to a diverse range of symptoms such as headaches, apnea, bradycardia, dysphagia, torticollis, spasticity, and impaired auditory evoked potentials [Wagner et al., 2002; Henriques Filho and Pratesi, 2006; Bowman and McLone, 2010]. Brainstem compression occurs in a third of patients with CII and may be fatal in about a third of these patients [Stevenson, 2004]. Surgical decompression of the posterior fossa for symptomatic CII is required in 8–17% of subjects with SBM [Wagner et al., 2002] and usually leads to clinical improvement. Maternal fetal surgery for SBM may also reduce the incidence and severity of brainstem dysfunction [Danzer et al., 2008].

Several eye movement abnormalities occur in CII including impaired smooth ocular pursuit, saccadic (i.e., fast eye movements) dysmetria, impaired performance of the vestibular-ocular reflex, various forms of pathological nystagmus (abnormal ocular oscillations), strabismus, and internuclear ophthalmoplegia (a type of gaze palsy that causes double vision) [Leigh and Zee, 2006]. Recording different classes of eye movements in CII has shed new light on motor function of the hindbrain in CII in relation to the anatomical changes in this malformation. Mid-sagittal vermis expansion, including the significant expansion of vermis lobules VI–VII area and preserved medial cerebellar volume corresponded to sparing of eye movements processed by the vermis, despite the overall reduction in cerebellar size that accompanies the deformity of CII [Salman et al., 2009]. These eye movement systems include saccadic accuracy, saccadic adaptation (a form of ocular motor learning), and smooth ocular pursuit [Salman et al., 2005, 2006b, 2007] In contrast, CII patients with abnormal ocular motor functions did not have a significantly expanded midsagittal vermis area. Furthermore, their midsagittal vermis area occupied a smaller midsagittal posterior fossa area, and their cerebellar volumes were smaller than in patients with CII, who had normal eye movements [Salman et al., 2009].

Therefore, the overall reduction in posterior fossa and cerebellar sizes in CII does not affect cerebellar structures or functions uniformly, because there is evidence for functional ocular motor circuits within the deformed hindbrain structures in many patients with CII. In addition, saccadic adaptation still occurred in CII despite the small and dysplastic cerebellum and was evident even in patients with eye movement abnormalities [Salman et al., 2006b, 2009]. Other types of motor learning have also been reported to be preserved in patients with CII including adaptation on reaching or ballistic movements, mirror drawing performance, and weight judgments [Colvin et al., 2003; Edelstein et al., 2004; Dennis et al., 2006a].

The Corpus Callosum

Even before sophisticated imaging methods became available for quantitative analyses of WM in SBM, aberrant development of the corpus callosum in 70–90% of SBM cases [Barkovich, 2005] made it a key focus of early qualitative imaging investigations. Dysgenesis of the CC is not a unique feature to SBM, and it also occurs in other neurogenetic syndromes [Ettinger, 1977]. Yet, along with hydrocephalus, CC dysmorphology was one of the earliest visible signs that incomplete neural tube closure at the level of the spinal cord had serious consequences extending beyond the tentorium.

As reported in qualitative studies of the CC, morphological variability is remarkable across individuals with SBM [Reigel and Rotenstein, 1994]. Although some of this variability may
be related to lesion level, lesion level does not account for all of the heterogeneity [Fletcher et al., 2005]. Recently, 26 regional patterns of CC morphology have been carefully documented in a sample of 193 children with SBM based on qualitative assessment of CC appearance across four subdivisions: rostrum, genu, body, and splenium [Hannay et al., 2009]. Whereas more than 50% of the study sample exhibited partial dysgenesis in either the rostrum (~21%) or splenium (~10%) or both regions (~22%), only 4% of the study sample had normal-appearing CC morphology across all four subdivisions. The remainder of the study sample did not exhibit any dysgenesis, but rather displayed various regional patterns of hypoplastic and normal appearing subdivisions of the CC.

In early quantitative MRI investigations of the corpus callosum in SBM, cross sectional area measurements were obtained from a single mid-sagittal slice in each participant [Fletcher et al., 1992, 1996; Hommet et al., 2002; Kawamura et al., 2002]. On average, the area measurement of the CC was small in children with SBM compared with controls. In all these studies, a diverse spectrum of CC morphology across SBM cases was reported; a majority of cases appearing to have normal CC size and morphology, and the majority of cases appearing abnormal with either hypoplastic features and/or partial agenesis. Consistent with a rostral-caudal developmental course of the CC [Barkovich and Norman, 1988], the genu was reported to be relatively well preserved in individuals with SBM, with hypoplastic features occurring in the body, and agenesis most prominent in the isthmus/splenium subregion [Kawamura et al., 2002].

Given the high incidence of posterior CC dysmorphology in individuals with SBM, it is not too surprising that significant deficits commonly occur in performance of cognitive tasks requiring recruitment of posterior networks, interhemispheric transfer, and transfer of language information [Huber-Okrainec et al., 2005; Dennis et al., 2006b; Hannay et al., 2008]. Thus, processing of semantic information is performed relatively easily, presumably due to a well-preserved genu as suggested by results of split-brain surgical patient studies [Sidis et al., 1981]. However, idiom comprehension is negatively impacted by hypoplastic CC morphology [Huber-Okrainec et al., 2005]. Even interhemispheric processing of simple auditory signals, as used in a dichotic listening task, is influenced by splenium dysgenesis, but not CC hypoplasia [Hannay et al., 2008].

The Cortex

Originally described nearly 20 years ago using pneumoencephalography and cerebral tomography imaging, posterior thinning of the cortical mantle in SBM was an important discovery that seemed to explain behavioral deficits in posterior network function [Dennis et al., 1981]. Using en bloc regional definitions in their volumetric analyses of structural MRIs, Fletcher et al. [2005] described significant reductions in both GM and WM volumes posterior to the genu of the corpus callosum in SBM. More recently, high-resolution surface-based cortical reconstruction analysis methods developed by Fischl and Dale [2000] have been used. This study reported significantly reduced cortical thickness in posterior regions and significantly increased cortical thickness in frontal regions based on group comparisons between an SBM group and healthy controls matched on age and gender [Juraneck et al., 2008]. These findings of altered spatial patterns of cortical thickening and thinning suggest a potential structural correlates of cognitive strengths and weaknesses generally exhibited by individuals with SBM.

Additional morphometry measures derived from surface-based analyses of the neocortex in individuals with SBM have included cortical GM volume and cortical complexity (e.g., gyrification). Using a 3D local gyrification index (LGI) measure of cortical complexity developed by Schaer et al. [2008], spatial patterns of cortical gyration have been contrasted with patterns of cortical thickness between a group of individuals with SBM ($n = 74$) and a comparison group of typically developing study participants ($n = 31$). As shown in Figures 4 and 5, inferior parietal and posterior temporal areas exhibiting cortical thinning are also characterized by increased cortical complexity. In frontal regions, SBM exhibits increased cortical thickness bilaterally in the following regions: inferior frontal, middle frontal, medial orbitofrontal, rostral anterior cingulate, and superior frontal. In bilateral inferior parietal and posterior temporal areas, the SBM group displays significant cortical thinning. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.].
White Matter Pathways: Diffusion Tensor Imaging Studies

Diffusion tensor imaging (DTI) provides a noninvasive measure of structural integrity of WM tracts. This MR modality capitalizes on the inherent properties of the motion of water. The averaged rate of diffusion and directionality of water movement can be quantified as mean diffusivity and fractional anisotropy, respectively [Basser et al., 1994]. Disruptions in WM integrity are reflected in mean diffusivity (MD) coefficients and fractional anisotropy (FA) measures despite the normal appearance of WM on routine MRIs. Because of the cylindrical geometry of neuronal fibers in WM, anisotropy is higher than in GM, where the cellular geometry is more globular. Thus, lower anisotropy values in WM are indicative of poor structural organization of WM tracts because highly organized fiber bundles constrain motion of water molecules in a preferred direction parallel to the orientation of the fiber tracts. Higher mean diffusivity values reflect poor structural integrity of WM because motion of water molecules is poorly constrained when cellular architecture of neuronal fibers is compromised [Beaulieu, 2002].

Using DTI acquisition and analysis methods, Vachha et al. [2006] investigated limbic tract anomalies in 13 children with SBM. The majority of children with SBM had atypical tractography results for the fornix (9/13) and cingulum (10/13). Although the fimbria of the hippocampus and the columns of the fornix were consistently intact in the SBM cases, the crura and the body of the fornix exhibited defects, frequently including thinning. Reconstruction of the cingulum was particularly challenging in SBM cases for the frontal–parietal, temporal, and preseptal segments, which were either absent or markedly hypoplastic [Vachha et al., 2006].

Hasan et al. [2008b] investigated DTI metrics of WM in several regions of interest, including the CC, arcuate fasciculus, and the anterior and posterior limbs of the internal capsule in 29 SBM children. In addition, the inferior longitudinal, inferior fronto-occipital, and uncinate fasciculi were evaluated in 38 SBM children [Hasan et al., 2008a]. Similar to investigations of other brain regions, a complex pattern of white matter (WM) differences between SBM and healthy controls has begun to emerge. In Hasan’s studies, group comparisons of some WM pathways exhibited no significant differences in fractional anisotropy (FA) measures (e.g., anterior and posterior limbs of the internal capsule, and the arcuate fasciculus), whereas other WM pathways were reported to have significantly lower FA values (e.g., genu of the CC, inferior longitudinal, inferior fronto-occipital, uncinate, and arcuate fasciculi). Thus, less-organized WM in SBM primarily occurs in the long association pathways linking posterior brain regions with anterior regions (e.g., inferior longitudinal and inferior fronto-occipital), which prove to be particularly difficult to track completely in SBM. However, the genu of the CC also exhibited significantly reduced FA values in SBM, indicating that commissural fibers between frontal regions are also compromised in SBM.

In another recent DTI study, Herweh et al. [2009] evaluated FA values from the CC and the anterior commissure in six SBM cases relative to a comparison group (n = 6) of age- and gender-matched healthy controls. Similar to Hasan et al. [2008a,b], these investigators also reported significantly reduced FA values of the genu in the SBM group. Additionally, the midsagittal area of the genu was significantly reduced in the SBM group. In their analyses of the anterior commissure, significantly increased midsagittal area was observed in the SBM group accompanied by a nonsignificant increase in FA. These contrasting differences between the genu of the CC and the anterior commissure in SBM are particularly enlightening since the anterior commissure develops in utero before the CC [Barkovich and Norman, 1988].

Although it is not yet clear whether hydrocephalus contributes to aberrant development of the corpus callosum [Gadsdon et al., 1979] or other WM pathways in SBM, it is quite clear that WM development is a protracted process that starts early in gestation, with changes in macro- and microstructure continuing throughout the lifespan. The vulnerability of WM to multiple insults at multiple developmental stages makes this particular tissue class a common candidate for investiga-
tions of neurological disorders. Because of tightly coupled developmental relationships between WM and GM, neither tissue class is altered in isolation; similarly, the cerebellum does not develop in isolation of the cerebral. In SBM, posterior cortex and the hindbrain exhibit complex structural differences in GM and WM properties relative to age-matched healthy controls. The anterior cortex, the genu of the corpus callosum, and the anterior commissure are structurally well suited for preservation of anterior network cognitive function.

CONCLUSIONS

As multimodal imaging studies continue to provide additional insight into the neurophysiological, structural, functional, and cognitive profiles of specific brain-behavior associations in SBM, accounts of strengths and weaknesses continue to provide essential clues for a better understanding of normal neurodevelopment and function. In addition to targeting specific structures (either GM regions or WM pathways) in hypothesis-driven research, network-level analyses will advance our understanding of neural circuit structure and function to account for connections between multiple structures underlying behavior.

REFERENCES


