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Introduction: Spina Bifida—A Multidisciplinary Perspective

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Spina bifida is the most common birth defect affecting the central nervous system (CNS) and is often characterized as the most complex birth defect compatible with survival [Liptak and El Samra, 2010]. Because of its complexity, the diagnosis and treatment of infants born with spina bifida begins before birth and through adulthood, involving multiple disciplines. Not surprisingly, research has flourished across several domains over the past decade. The purpose of this special issue of *Developmental Disabilities Research Reviews* is to systematically review research on spina bifida within different domains in an effort to promote integration and awareness of this research across disciplines involved directly with spina bifida. In addition, we hope to increase the awareness of contemporary research and treatment strategies for researchers and practitioners involved with other developmental disabilities. Although some aspects of spina bifida have been reviewed as part of previous issues, this is the first issue of the journal specifically devoted to spina bifida since an issue on neural tube defects edited by Sells [1998].

In addition to specific articles that summarize a body of research, a feature of this special issue is the inclusion of articles on current treatment approaches and health care outcomes and needs of children and adults with spina bifida. These approaches, which involve multiple disciplines, have evolved over the last two decades due to the experience and advocacy of experienced practitioners. As several papers in this issue suggest, there is a need for multicenter studies of health, psychosocial, and education intervention issues affecting people with spina bifida, which would also facilitate genetic and other fields of research. It is important to do this research because what is learned about spina bifida, which is more prevalent than many other neurogenetic disorders, can impact treatment for people with other developmental disabilities. The issues of transitioning to the adult health care system affect many people with a broad range of developmental disabilities [Liptak and El Samra, 2010; Sawyer and MacNee, 2010]; understanding phenotypic variations in cognition and brain function across neurogenetic disorders may help identify endophenotypes and facilitate identification of more general strategies for facilitating learning and independence [Dennis and Barnes, 2010].

SPINA BIFIDA AS A NEURODEVELOPMENTAL DISORDER

Spina bifida is a neurogenetic disorder with a complex etiology that involves genetic and environmental factors. The most common form of spina bifida, myelomeningocele is often used interchangeably with spina bifida. Myelomeningocele usually (but not always)

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affecting the brain with characteristic phenotypic features that involve cognition, behavior, and adaptation, along with the more recognized complex effects of neurological dysfunction on multiple organ systems. Unlike other neurogenetic disorders that involve genes, brain, and behavior, spina bifida myelomeningocele is less commonly viewed as a neurogenetic disorder, even though modal cognitive and behavioral phenotypic features share some striking similarities with other congenital developmental disorders [Dennis and Barnes, 2010], such as the preservation of certain speech and language characteristics, hypersociality, good word reading, but poorer development of language/reading comprehension, and math. However, these features vary with the individual in a principled manner. Intellectual disabilities are infrequent and the most common outcomes involve strengths and weakness in cognitive, academic, behavioral, and adaptive skills.

The public perception remains one in which spina bifida is viewed as an orthopedic disorder because of the difficulties with ambulation that are readily apparent, the strengths in language and social skills that characterize many with spina bifida, and the fact that some less frequent forms of spina bifida are not associated with brain anomalies. In public schools, classification for special education is most often as an orthopedic impairment and learning difficulties are still attributed to motivational and behavioral factors even though most people with spina bifida myelomeningocele have congenital malformations of the brain and hydrocephalus [Del Bigio, 2010; Juranek and Salman, 2010]. In this respect, spina bifida is a remarkable example of neural plasticity given the preservation and development of skills and adaptive abilities despite a cascade of adverse events beginning with the early formation of the neural tube, which should lead to intense scientific study of the mechanisms underlying this plasticity. In addition, spina bifida requires more specialized medical and rehabilitative treatment than is typical of many neurogenetic disorders [Liptak and El Samra, 2010; Webb, 2010], with its treatment impacting how other chronic disorders with one or more shared features (e.g., hydrocephalus) might be treated.

CHANGING FACE OF EPIDEMIOLOGY

In different articles in this issue, readers will see slightly varying estimates of the prevalence of spina bifida largely because the prevalence of neural tube defects is declining in North America and Western Europe because of dietary fortification and also because of advanced prenatal diagnosis that is leading to more elective terminations [Au et al., 2010; Bowman and McLone, 2010]. Prenatal diagnosis involves alpha-fetoprotein screening and ultrasonography in neural tube defects because definitive chromosomal abnormalities are usually not present [Au et al., 2010]. To illustrate, Williams et al. [2005] reported a postdietary fortification rate of 2.62 per 10,000 live births from 1995 to 2002 (with prefortification rates at 5–10 per 10,000), with variation across birth cohorts that led to an overall estimate of 3/5 per 10,000 births; in a follow-up, Boulet et al. [2009] reported a decline to 2.02 per 10,000 live births. The 2.62 and 2.02 estimates are based on birth certificates, which are known to underestimate the prevalence of birth defects and the difficulty in precisely estimating the impact of planned terminations.

The termination issue is sensitive and its impact on prevalences is unclear. Which of these factors is most important is not known because reasons for termination are not recorded. In a study of the Houston-Galveston metropolitan area/lower Rio Grande Valley [Waller et al., 2000], parents infrequently terminated fetuses with nonlethal defects, with spina bifida showing a 7–10% termination rate compared with a 36% termination rate for anencephaly. Some parts of the country likely continue to show a low frequency of terminations. However, these kinds of decisions may be changing with time. In a study of terminations in the offices of perinatologists in metropolitan Atlanta, Cragan and Gilboa [2009] reported a significant increase in terminations across multiple disorders from 1995 to 2004, with

anencephaly well over 50% and spina bifida about 35%. Prenatal diagnosis seems to be the most relevant factor in these changes and affect all disorders for which prenatal screening is available. Common attributions of decisions about termination that involve religion, cultural factors, or poverty are not accurate. Jones et al. [2002] reported that women 18–29 years of age, unmarried, black or Hispanic, or economically disadvantaged have the highest rates of elective termination. Minnis and Padian [2001] reported that US-born Hispanic women are most likely to have had a terminated pregnancy compared with other ethnic subgroups of US-born non-Latina women.

Despite these findings, spina bifida is not going away as a common congenital birth defect. The prevalence in many parts of the world is higher than in North America. Moreover, even if every woman of child-bearing age in the US took dietary supplements, fortification would prevent about 50–70% of neural tube defects [Hall and Solehdin, 1999]. Unfortunately, knowledge does not always change behavior. A recent CDC survey reported that 61% of women ages 18–24, 87% of ages 25–34, and 89% ages 35–45 knew about dietary factors in preventing neural tube defects. However, taking supplements containing folic acid was reported in 30% in the 18–24 year age group, 47% in 25–34 year olds, and 40% of those between 35–45 years old [Centers for Disease Control, 2008]. Additional births involving spina bifida have been documented in families with previous births who were taking dietary supplements. Not only is spina bifida not going to disappear but also there are still several thousand pregnancies involving spina bifida every year. Most importantly, according to recent Centers for Disease Control estimates, as many as 166,000 people with spina bifida live in the United States [see Liptak, 2010]. There is an urgent need to develop a comprehensive research program focusing on people with spina bifida, which will also have important implications for enhanced scientific understanding and treatment of other neurodevelopmental disabilities.

SPINA BIFIDA IS A HETEROGENEOUS DISORDER

Some of the confusion about the nature and prevalence of spina bifida involves its multiple sources of phenotypic variability. The characteristic spinal dysraphism at birth that identifies spina bifida (literally “split spine”) is not a uniform lesion and includes myelomeningocele, meningocele, lipomyelomeningocele, and occulta. Myelomeningocele, in which the spinal cord protrudes through an incompletely fused spine, is the most common and most severe, accounting for 80–90% of all births. Meningocele is infrequent and does not have protrusion of the spinal cord, but does have incomplete fusion of the vertebrae. Sometimes fatty tumors (lipomas) are incorporated with myelomeningoceles (or more rarely, meningoceles). Occulta represents one of several spinal defects that are covered and are often asymptomatic, affecting many more people than the other three types of spinal dysraphisms. Occulta is usually not detected by prenatal diagnosis, not included in estimates of the prevalence of spina bifida, may involve different causal factors, and are usually indentified because the person develops urologic or back problems. For the other forms of spina bifida, the level of the spinal lesion clearly affects function, almost always leading to impairment of the lower extremities, a neurogenic bladder [Clayton et al., 2010], and other orthopedic complications [Thomson and Segal, 2010]. A general principle is that the higher the spinal dysraphism, the greater the orthopedic impairment. In addition, in myelomeningocele, higher level defects are associated both with greater severity of brain malformations and poorer cognitive and motor outcomes, most likely because of greater impairment in brain structure [Fletcher et al., 2005]. Lesion level also accounts for genetic heterogeneity, as does ethnicity and socioeconomic status [Au et al., 2010]. Whether genetic factors directly influence cognitive outcomes and brain structure in spina bifida is largely not addressed, but may explain some of the variability in outcomes.

One reason that identification of the type of spinal dysraphism is important is that only myelomeningocele is characteristically associated with brain malformations. The malformation of the cerebellum and hindbrain known as the Chiari II malformation occurs in over 90% of people with myelomeningocele [Juranek and Salman, 2010]. Dysgenesis of the corpus callosum involving the rostrum, splenium, and posterior body, or both, is also frequent and likely congenital because the ends of the corpus callosum are affected [Barkovich, 2005]. Variations in the integrity of both the cerebellum and corpus callosum clearly affect cognitive functions, behavior, and adaptation in people with myelomeningocele in a principled manner [Dennis and Barnes, 2010; Juranek and Salman, 2010].

The other CNS factor that affects cognitive functions, behavior, and adaptation is hydrocephalus, and its treatment. Some form of ventriculomegaly is usually present in people with myelomeningocele because of the obstruction caused by the Chiari II malformation, and in some people with myelomeningocele or other spinal dysraphisms, because of aqueductal stenosis [Del Bigio, 2010]. Shunt diversion, which began in the 1970s, has been credited with increasing the survival rate of people with myelomeningocele [Liptak and El Samra, 2010]. At one point, it was routine to repair the spinal lesion and implant a shunt for myelomeningocele. However, because of concerns about the long-term effects of shunt diversion due to malfunction and infection [Bowman and McLone, 2010], many centers now implant shunts at birth only when there is significant ventricular dilation and monitor ventricular dilation over time with serial neuroimaging monitoring of development.

There is concern about the effects of this decision, especially because animal models of hydrocephalus, which do not exactly replicate hydrocephalus in spina bifida, show restoration of white matter with treatment and impairments in white matter and learning with persistent hydrocephalus [Del Bigio, 2010]. Regardless of the factors underlying improved outcomes, people with spina bifida now commonly survive well into adulthood. Although specialty treatment clinics are common for children with spina bifida [Liptak and El Samra, 2010], the transition to adult health care is a major issue [Sawyer and MacNee, 2010] and the psychosocial and health care needs of adults are different from those of children [Webb, 2010]. The efficacy of fetal surgery in preventing the Chiari II malformation and hydrocephalus, and improving urologic functions, is the subject of a NICHD-sponsored randomized trial for which results are not available.

If there is a single defining characteristic of people with spina bifida, it is variability in needs and outcomes. This is apparent in studies of health related quality of life [Sawin and Bellin, 2010] and psychosocial outcomes [Holmbeck and Devine, 2010], cognitive outcomes [Dennis and Barnes, 2010], the brain [Del Bigio, 2010; Juranek and Salman, 2010], and even in genetic and environmental factors related to the multifactorial causes of spina bifida [Au et al., 2010]. To fully understand spina bifida will require studies with larger samples and multiple disciplinary perspectives, which will require multiple institutions working together. The articles in this special issue were designed to build upon the need for a multidisciplinary perspective that recognizes the variability in outcomes. This issue builds upon the First World Conference on Spina Bifida Research and Care [Liptak, 2010], which provided an opportunity for researchers and practitioners from around the world to discuss approaches to improving the care of people with spina bifida. This issue, in which most of the authors were also involved in this meeting, provides an opportunity to summarize research findings and contemporary treatment approaches in depth and in multiple domains. The World Congress followed a meeting in May, 2003, that involved about 100 experts who discussed a research agenda for evidence-based practices involving spina bifida [Liptak, 2004]. By placing research and treatment issues in a peer reviewed journal, we hope to

communicate the current status of research and practice on spina bifida with professionals in other areas involving developmental disabilities. In addition, we hope to increase awareness and future research among people involved with spina bifida, thus leading to increased opportunities to integrate findings across disciplines.

OVERVIEW OF ARTICLES

The first 5 articles in this issue address genes, brain, and cognition/behavior. Au et al. [2010] review current research on the epidemiology and genetics of spina bifida and other neural tube defects, showing substantial progress since the previous review of this area in *Developmental Disabilities Research Reviews* [Hall and Solehdin, 1999]. They highlight the important insights that epidemiological research has provided, particularly in terms of approaches to prevention and the impact of dietary fortification. They identify multiple sources of potential candidate genes, including folate and glucose metabolism, cellular functions, brain development, and animal models. Of an estimated 132 candidate genes, 42 have been associated with neural tubes defects. Au et al. note that many studies are underpowered and that large samples are needed to detect small gene effects, especially in a multifactorial disorder like spina bifida, so that researchers are not able to take advantage of newer methods for identifying genetic associations, such as genome wide association (GWAS). Echoing a theme across several papers, they call for multi-institutional collaborative studies.

Del Bigio [2010] provides a review of the effects of hydrocephalus on brain development, structure, and function. Drawing from human studies, animal models, and postmortem studies, he identifies the effects of ventricular enlargement on the periventricular white matter, noting effects on multiple systems. He also identifies effects of hydrocephalus on learning and memory, observing that in animal models, some effects on the brain are reversible, but destroyed axons cannot be restored. Del Bigio recommends further investigation of animal models as well as human outcomes, both in relation to outcomes involving learning and behavior, as priority areas for research, along with additional postmortem studies.

Juranek and Salman [2010] review studies of brain structure and function in myelomeningocele, summarizing different theories of the Chiari II malformation and its effects on a range of cerebellar functions. They also review recent studies of brain structure using quantitative MRI, identifying distinctive features of the brain in myelomeningocele, especially the tendency for preserved or enlarged anterior regions, and thinned posterior regions. They highlight the importance of multimodal imaging studies in relation to cognitive and behavioral outcomes as especially important areas for research.

Dennis and Barnes [2010] evaluate research on cognitive functions in myelomeningocele. They note that myelomeningocele does present with characteristic cognitive strengths and weaknesses that are not domain specific (e.g., preserved language versus impaired spatial cognition). However, they argue that cross domain patterns occur within cognitive domains but represent the operation of more general principles that involve strengths in cognitive areas in which the information is fixed or stipulated (e.g., vocabulary, word reading, categorical perception) versus constructs in which the information must be assembled or constructed (e.g., language/reading comprehension, figure-ground perception). Dennis and Barnes [2010] highlight the importance of a research agenda that moves away from traditional psychometric tests toward experimental tasks that are more directly related to brain structure and function in order to facilitate development of effective interventions. In addition, they emphasize the importance of comparisons of cognitive and brain functions across developmental disorders.

Holmbeck and Divine [2010] summarize psychosocial and family research across the lifespan involving spina bifida. They present a bio-neuropsychological model to explain variation in psychosocial and family functioning that supports a resilience-disruption view. Thus, while a child with spina bifida often disrupts the family, this disruption can be moderated depending on how the family adapts. Children with spina bifida are at high risk for psychosocial and behavioral difficulties, with the level of risk increasing they become adults. They call for research that is longitudinal and theory-driven, with a particular need for randomized controlled trials of family-based interventions.

The remaining seven articles focus more directly on issues related to health care, transition, and quality of life in persons with spina bifida. All of these areas have been insufficiently studied and will require increased research attention and funding to address the many research questions that have been identified by the authors. A special effort was made in this edition on spina bifida to focus attention on research that is moving to increasing importance for all neurodevelopmental disabilities and particularly for spina bifida quality of life, survival into adulthood and an aging population, and the changing face of health care delivery. Not every issue involving care could be discussed in the confines of this special issue; for the more clinically oriented healthcare-related articles, the authors have underscored the status of research around the most important aspects of clinical management and areas where changes or controversies in treatment have occurred in recent years.

Moving away from a model of focusing on strictly medical aspects of care, there has been increasing effort to evaluate and support quality of life in individuals with spina bifida. Sawin and Bellin [2010] note that this may be particularly challenging in persons with spina bifida due to the impact of complex medical and environmental factors on quality of life. As there is a wide body of research literature examining quality of life in chronic conditions, there is relatively little literature that focuses specifically on spina bifida. This article begins with a discussion of conceptual and methodological issues, and moves to a synthesis of quality of life research involving spina bifida. The authors outline challenges in applying currently existing quality of life instruments in the assessment of people with spina bifida. The authors suggest that future research should be directed at multisite, longitudinal studies that include children across the developmental span, including adults. In addition, they recommend further research into improving quality of life assessment instruments, research that focuses on the influence of contextual factors contributing to quality of life, and research into interventions to enhance quality of life. This review clearly addresses issues that pertain to all neurodevelopmental disabilities.

As individuals with spina bifida now more routinely live into adulthood, the effective transition of care from pediatric to adult settings is increasingly important. However, Sawyer and MacNee [2010] report that while the goal of transition to adult health care is to maximize functioning and potential through the provision of high quality, uninterrupted care throughout life, the development of models of health care for adults with spina bifida lags behind those of other chronic health conditions. They note the challenge of delivery of adult services to persons with spina bifida, but advocate study of existing models of health care delivery to adults and barriers to successful transition of care. In addition, they highlight the need for clinical leadership to generate a culture of quality improvement surrounding care delivery throughout the lifespan.

Echoing the articles on quality of life and transition issues, Liptak and El Samra [2010] highlight the challenges of health care delivery and the lack of focus in current research on incorporation of activities and societal participation of persons with spina bifida. The authors reference disease management models from other pediatric chronic diseases as examples with lessons that might be applicable to spina bifida. They note the importance of

studying not just direct health care delivery, but also of organizational structure and support, governmental policies, payors, and regulations in order to fully impact health outcomes in spina bifida. In the second part of their article, they look at research on nonsurgical medical issues in children with spina bifida. They list a number of areas for which research is needed, including patient-focused, evidence based care, quality improvement initiatives, and study of systems of care that incorporate evaluations of the fiscal impact of care.

Recognizing the importance of health care throughout the lifespan, the article by Webb [2010] focuses specific attention on health care issues for adults with spina bifida. Because the article provides some information about more direct spina bifida health issues, Webb focuses attention on the issues of age-related secondary conditions and general adult health care needs as they interface with spina bifida. Particularly noteworthy are sections on research into cardio-pulmonary issues, sexuality and obesity with its attendant complications —all important issues from both an individual and societal perspective. Webb notes that research related to adults with spina bifida come mostly from case reports or small series of participants, and that almost no literature is published about later adult ages. He calls for research that is multisite, and which incorporates patients in the fourth, fifth, and sixth decades.

In their article on the neurosurgical management of spina bifida, Bowman and McLone [2010] note that as the ventriculo-peritoneal shunt revolutionized care and led to increased survival of individuals with spina bifida, morbidity associated with shunts is leading many to rethink the assessment and management of ventriculomegaly and hydrocephalus. In addition, the importance of longitudinal surveillance and management of neurosurgical issues to reduce medical and functional decline is mentioned. In particular, the challenge of a tethered spinal cord, also discussed by Thomson and Segal [2010] and Clayton et al. [2010], is problematic and understudied. Because of the impact of various neurosurgical issues on other organ system and cognition, Bowman and McLone call for multi-center randomized trials to develop stronger evidence-based approaches to neurosurgical management.

Perhaps no other area of medical management of spina bifida has received as much attention as the urologic issues. The impact of the neurogenic bladder on morbidity and the challenges of incontinence (of cardinal importance to individuals with spina bifida because few avoid some type of bladder difficulties) have led to a variety of interventions. Unfortunately, as Clayton et al. [2010] observe current interventions have shown clinical effectiveness, but there is still wide variability in clinical practice. Many interventions are not supported by strong evidence-based research. The authors also note the importance of long-term clinical follow-up to address urologic issues and describe the need for research into current management and novel treatment ideas that are multisite and collaborative among neurosurgeons and urologists. In addition, they highlight a need to promote research which focuses on social continence and quality of life, echoing Sawin and Bellin [2010].

In their review of the orthopedic management of spina bifida, Thomson and Segal [2010] write that there has been increasing attention to functional status in persons with spina bifida, and therefore, increased use of gait analysis and emphasis related to the importance of the function of the knee. There has also been improving awareness of the impact of underlying spasticity, balance difficulties, and tethered cord on functional status. Scoliosis and kyphosis remain challenging issues and the authors summarize the available treatment research, but note relatively poor levels of evidence for evaluating the various management strategies for spinal deformities. The authors call for evidence-based research in all areas of orthopedic management that focuses not just on operative procedure results, but also incorporates use of functional outcome measures.

FINAL THOUGHTS

The goals of this special edition of *Developmental Disabilities Research Reviews* have been to inform about and increase interest in research in spina bifida. Where do we go from here? From articles addressing the etiologies of spina bifida, brain/behavior relationships, specific medical issues, and contextual influences of family, school, society, and health care delivery, the undercurrent theme is that more research is needed—research that multi-site, collaborative, encompasses the lifespan, and incorporates functional assessment, measures of activities, societal participation, and quality of life of persons with spina bifida as important components. The authors of these articles suggest many specific areas that are ripe for research and that can have implications (both specifically and broadly) for other neurodevelopmental disorders. However, the key is to work across disciplines. In the first issue of *Developmental Disability Research Reviews*, the editor, Mark Batshaw, stated that "no single medical specialty or discipline provides insight into the problems of all affected individuals" [Batshaw, 1995, p 1]. He further observed that "arriving at solutions to problems of development requires the tools and expertise of an array of disciplines …"; [Batshaw, 1995, p 1]. Spina bifida epitomizes these observations, representing a complex, multifactorial neurodevelopmental disorder that cuts across multiple disciplines. Although research and practice within disciplines is clearly important, working across disciplines and across disorders is likely to enhance research and practice with spina bifida. As Wilson [1998] summarized in *Consilience*, advances in science may occur at the boundaries of disciplines. Large samples, of course, facilitate interdisciplinary research.

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