REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

Spina Bifida

Bermans J. Iskandar, M.D., and Richard H. Finnell, Ph.D.

From the Department of Neurological Surgery, University of Wisconsin–Madison, Madison (B.J.I.); and the Departments of Molecular and Human Genetics, Molecular and Cellular Biology, and Medicine, Baylor College of Medicine, Houston (R.H.F.). Dr. Iskandar can be contacted at iskandar@neurosurgery.wisc.edu or at University of Wisconsin Hospital and Clinics, 600 Highland Ave., K4/832, Madison, WI 53792.

N Engl J Med 2022;387:444-50.
DOI: 10.1056/NEJMra2116032

CME at NEJM.org

Spina bifida is a developmental malformation of the spinal cord that leads to complications in several organ systems and considerable disability, even decades after repair of the anomaly. Before the 20th century, less than 20% of children with spina bifida survived to adulthood, a survival rate that has been improved with the use of safe anesthesia and aseptic surgical techniques and the development, in the 1950s, of ventricular shunts for elevated intracranial pressure. Recent public health measures supporting folate supplementation in women of child-bearing potential have greatly decreased the incidence of the disorder. Surgical approaches directed at ameliorating neurologic complications, together with multispecialty care, have further improved survival and quality of life for children with spina bifida. As a result, most persons now living with spina bifida are adults,[1] and the challenge for health care providers is to make sure that adult programs can deliver the same care from which patients benefit in childhood.

Pathophysiology

Failure of the neural tube to fuse during the third week of gestation leads to an open neural-tube defect at the cranial level (anencephaly), the spinal level (myelomeningocele or, simply, spina bifida), or both (craniorachischisis).[2] Anencephaly and craniorachischisis are lethal during gestation or soon after birth. A myelomeningocele is an open defect consisting of a malformed spinal cord that has no dura, bone, muscle, or skin coverage, with associated susceptibility to infection and cerebrospinal fluid (CSF) leakage. Incomplete formation of the lower spinal cord causes leg, bladder, and bowel dysfunction. Although experimental evidence confirming any of the many proposed pathophysiological causes is lacking,[3] the assumption has been that the open spinal defect and associated CSF leakage in utero can cause lack of distention of the primitive cerebral ventricular system, leading to anatomical intracranial abnormalities,[4] including herniation of the cerebellar vermis and medulla into the spinal canal (Chiari II malformation). The Chiari II malformation, in turn, obstructs the flow of CSF around the lower brain stem, causing ventricular dilatation with increased intracranial pressure (hydrocephalus) and cystic dilatation of the spinal cord (syringomyelia), with brain-stem and upper spinal cord dysfunction.[4] Months or years later, scarring (arachnoiditis) of the myelomeningocele repair site may result in traction on the spinal cord, leading to a tethered cord in at least a third of patients, with symptoms that include back and leg pain and worsening leg, bladder, and bowel function. Repeated surgery is often required to release the spinal cord from surrounding scar tissue. Postoperative tethering is distinguished from "congenital" tethered cord syndrome in patients born with spinal abnormalities, in which skin covers the defect; these abnormalities include tight filum terminale, dermal sinus tract, and split cord malformation.

GENESIS AND PREVENTION

Neural-tube defects are considered to arise from a complex relationship between genomic and environmental factors, including maternal diabetes, hyperthermia, anticonvulsant agents, obesity, and toxins.[1] No single gene has been identified that causes isolated neural-tube defects. Multiple genomic sequence variations contribute to these defects, but it has not been possible to estimate susceptibility on the basis of individual variants, and rodent models fail to replicate the diverse features of the human disorder.[1]

Evidence indicates that neural-tube defects result in most cases from acquired and heritable disorders of the folate pathway that are largely preventable with dietary folate supplementation.[1] Periconceptional administration of folic acid (a synthetic — and the most commonly used — form of folate) in the mother has reduced both the first occurrence of fetal open neural-tube defects (i.e., in women who had never had an affected pregnancy) and the subsequent occurrence of fetal open neural-tube defects (i.e., in women who had previously had an affected pregnancy) by at least 70%.[5,6] The U.S. Public Health Service recommends that women of reproductive age consume folate daily[7,8] and mandates that certain foods be fortified with folic acid.[9,10] Coordinated public health efforts have led to a sharp decline in the prevalence of spina bifida in North America and in most upper-middle-income and high-income countries, which is now approximately 34 to 37 cases per 100,000 live births.[9] Despite the low cost and widespread accessibility of folate, food fortification efforts are stalled in many countries, in part because of a lack of governmental action. In these regions, the prevalence of the disorder is approximately 54 to 87 cases per 100,000 live births, with a prevalence as high as 300 per 100,000 in the mostly low-income regions where spina bifida is endemic.[9-11]

Although efforts are under way to address disparities in food fortification,[10] complete prevention has not been attained, even in areas with established folate fortification programs,[12] and neural-tube defects remain one of the three most common severe birth defects, along with congenital heart disease and Down syndrome (also called Down's syndrome). Thirty percent of cases occur despite supplementation, and mouse models of neural-tube defects that do not respond to folate treatment (i.e., "folate-resistant" neural-tube defects) have been identified.[1] Folate dose–response studies in human populations have not been performed, and the required maternal dose and target blood levels of folic acid for prevention are unknown. Although it is unlikely that any specific dose of folic acid is optimal for all pregnancies, only one case–control study[13] and another study using complex statistical modeling[14] have attempted to correlate the risk of neural-tube defects with maternal red-cell folate levels. Progress in the prevention of neural-tube defects depends on addressing access to folic acid and disparities in such access and answering remaining questions about the type and dose of folate supplements, the consequences of oversupplementation, paternal as well as maternal risk factors associated with neural-tube defects, and the correlation between environmental exposures and genetic or epigenetic predispositions.

EARLY CLINICAL PRESENTATION

The neurologic presentation of the newborn with spina bifida depends on the spinal level of the defect. An infant with a low sacral myelomeningocele may have normal findings on neurologic examination, whereas infants with higher lesions (e.g., in the lumbar or thoracic spine) may present with neurogenic bladder and various degrees of lower-extremity sensorimotor deficits, from foot weakness in low lumbar myelomeningocele to paraplegia in thoracic myelomeningocele. In such cases, shortly after birth, computed tomography or magnetic resonance imaging of the head is performed to rule out hydrocephalus, which may be manifested as a bulging fontanelle, macrocephaly, and neurologic symptoms. The patient's cardiac status and general medical status are evaluated to rule out other congenital anomalies that would need to be incorporated into a comprehensive care plan for neonates and infants. Ultrasonography and bladder catheterization are used to assess urologic function. The patient is examined for evidence of foot, leg, or hip deformities that might require early orthopedic interventions.

Table 1. Evidence for the Treatment of Spina Bifida.*

Class I evidence

Prenatal surgery for myelomeningocele in patients who meet MOMS criteria reduces the risk of shunt-dependent hydrocephalus.

Class II evidence

Ambulation improves in the short term after prenatal repair but may deteriorate over time after prenatal or postnatal repair, as a result of tethered cord syndrome.

The rate of tethered cord syndrome and inclusion cysts among infants who have undergone prenatal myelomeningocele closure is the same as or higher than the rate among infants who have undergone postnatal closure; both groups require long-term surveillance.

Class III evidence

There is insufficient evidence that myelomeningocele repair within 48 hours after birth decreases the risk of wound infection or ventriculitis.

Antibiotics should be given if surgery is going to be delayed for more than 48 hours after birth.

There is insufficient evidence to conclude that ventricular size and morphologic features affect neurocognitive development.

* Data are from the Congress of Neurological Surgeons guidelines.[15] MOMS denotes Management of Myelomeningocele Study; criteria for enrollment included maternal age of 18 years or older, maternal body-mass index (the weight in kilograms divided by the square of the height in meters) less than 35, gestational age between 19 and 26 weeks, a normal karyotype, and U.S. residency. Major exclusion criteria were fetal anomaly other than myelomeningocele, risk of preterm birth, placental abruption, and contraindications to surgery (e.g., previous hysterotomy).

MANAGEMENT

The surgical care of a patient with spina bifida starts with repair of the myelomeningocele to prevent CSF leakage, meningitis, and scarring of the open defect, with treatment of hydrocephalus to minimize the risks of intellectual disability and death (Table 1). The neural placode is a flat segment of spinal cord that fails to form a tube during primary neurulation. Together with an attached thin epithelial membrane, the placode forms the exposed wall of a fluid-filled myelomeningocele sac. This exposed wall requires a layered repair, including closure of the dura, muscle or fascia, and skin over the exposed placode (Fig. 1).

PRENATAL MYELOMENINGOCELE REPAIR

Spina bifida can be diagnosed by means of ultrasonography during the second trimester of pregnancy. On the basis of promising findings in animal models and retrospective clinical studies, a prospective, randomized trial, the Management of Myelomeningocele Study (MOMS), was conducted, with criteria for enrollment that included maternal age of 18 years or older, maternal body-mass index (the weight in kilograms divided by the square of the height in meters) less than 35, gestational age between 19 and 26 weeks, and a normal karyotype.[16] The study showed better outcomes with prenatal than with postnatal repair of a myelomeningocele. Infants who had undergone prenatal repair had improved motor function of the legs and feet at 30 months, with a lower incidence of hydrocephalus (40%, vs. 82% with postnatal repair) and Chiari II malformation (64% vs. 96%) at 1 year. The risks associated with prenatal repair included premature rupture of membranes and uterine rupture in subsequent pregnancies,[17] as well as fetal complications of premature birth, intraspinal inclusion cysts, and tethered cord syndrome.[18] Subsequent analyses of a subgroup of the participants in the MOMS (MOMS2), conducted when the children were between 5 and 10 years of age, showed better mobility, neuropsychological test scores, and independent functioning in the prenatal repair group than in the postnatal repair group.[19]

Many questions about this procedure remain unanswered. Will the benefits of prenatal repair be durable? As more centers offer the procedure, will the MOMS results be replicated despite differences among centers in case volumes, surgical experience, and surgical techniques? Would improvements in fetal surgery techniques, such as the increasingly popular fetoscopic approaches,[20] replicate the MOMS results while reducing maternal and fetal complications? How will the costly and technologically demanding procedure affect access to and disparities in care?

MEDICAL PROBLEMS ASSOCIATED WITH SPINA BIFIDA

Functional neurologic decline in a patient with spina bifida is infrequently the result of the natural history of the disorder and prompts an evaluation for a surgically correctable abnormality or complication (e.g., hydrocephalus, Chiari II malformation, syringomyelia, or a tethered spinal cord) or a medical complication such as urinary tract infection or constipation, which may temporarily exacerbate the underlying neurologic deficit or shunt function. The challenge that neurosurgeons face when caring for a symptomatic patient with spina bifida is the overlap in symptoms between these surgical and medical problems.

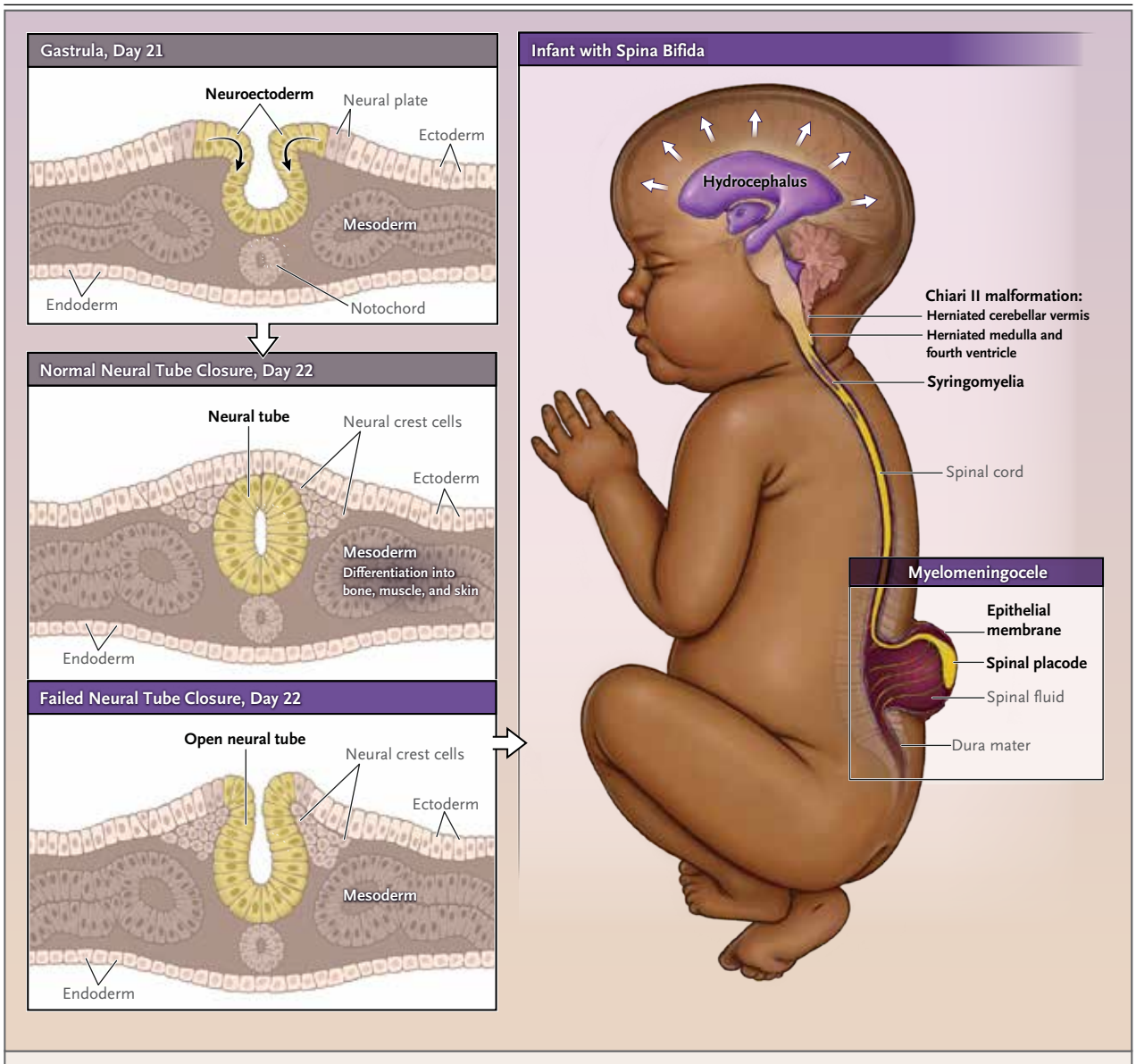

Figure 1. Diagrams of Normal and Failed Neurulation and an Infant with Spina Bifida.

Primary neurulation (left) is the process by which the neural plate folds into a tube to form the brain and the spinal cord. Failure of the caudal neural plate to neurulate results in a myelomeningocele (spina bifida). The diagram of the infant with spina bifida (right) shows an unrepaired myelomeningocele, a Chiari II malformation, and cervical syringomyelia. The white arrows show that the cerebral ventricles are enlarged from increased intracranial pressure, resulting in hydrocephalus. Hydrocephalus in infants causes increased head circumference and a bulging fontanelle (not shown).

Hydrocephalus is a major cause of neurologic disability and death in children and adults with spina bifida. Conventional treatment for hydrocephalus is ventriculoperitoneal shunting, which has a 30 to 40% failure rate at 1 year,[21-23] with a substantial risk of complications and death. Endoscopic third ventriculostomy has emerged as an alternative to shunting for some patients. Combined with endoscopic choroid plexus coagulation, in which the choroid plexus is electrosurgically ablated, endoscopic third ventriculostomy led to shunt independence in more than 70% of patients in a prospective study involving 115 Ugandan infants with spina bifida.[24] A multicenter study to investigate efficacy beyond East Africa is under way (ClinicalTrials.gov number,

NCT04177914). The combined procedure has become an option for infants with spina bifida, but it does not appear to be beneficial when performed in older children or adults. Nevertheless, most patients who are living with spina bifida have shunts, and malfunction of the shunt is suspected when there are new neurologic symptoms, regardless of the size of the ventricles on imaging. Lower-cranial-nerve and respiratory symptoms attributed to Chiari II malformation, at one time considered to be the most common cause of death in children with spina bifida, may be an indirect manifestation of elevated intracranial pressure from undetected ventriculoperitoneal shunt malfunction, even in the absence of ventricular dilatation on imaging.[25,26] Although previously favored, posterior fossa decompression surgery for Chiari II malformation has been largely supplanted by shunt revision.[27]

Studies of the perspectives of persons with spina bifida and their families, performed in collaboration with patient advocacy groups, have helped to promote consideration of the health experience of patients with spina bifida and have prompted the publication of consensus-based guidelines by the Spina Bifida Association and its physician partners (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[28] The Centers for Disease Control and Prevention has established a registry for system-specific management of spina bifida, which has generated specialty-specific quality-improvement protocols and publications (https://www.cdc.gov/ncbddd/spinabifida/nsbprregistry.html).

There is consensus about the role of urologists in the early management of spina bifida; the aim is to prevent neurogenic bladder from causing kidney and ureter damage, including retention, incontinence, and urinary tract infections.[29] The introduction of clean, intermittent catheterization in the 1970s led to expectations of full social continence and retained kidney function in patients with spina bifida, with recent reports suggesting that pharmacotherapy can help to relax bladder detrusor smooth muscle and increase capacity.[30,31] There remains a role for operative reconstruction of the dysfunctional bladder and assistance with achieving urinary continence. Despite advances in the management of spina bifida, half the parents of children with the condition rate bowel incontinence as their child's biggest issue,[28] and dissatisfaction with sexual function is common later in life.

Orthopedic and physical medicine care are essential for foot deformities or contractures that affect standing, transferring from or to a wheelchair, or walking, as well as for scoliosis and hip and limb contractures, which require extensive physical therapy and surgery to improve sitting and positioning. Skin breakdown from pressure over insensate regions or from incontinence, a high prevalence of latex allergy, nutritional challenges and obesity, sleep-disordered breathing, and cognitive problems also affect the quality of life of patients and the prospects of independence.

TRANSITION FROM PEDIATRIC TO ADULT CARE

Because of the preventive, medical, and surgical successes of past decades, most of the estimated 166,000 persons in the United States who are living with spina bifida are adults.[1] The Spina Bifida Association has suggested that the expertise and organized multidisciplinary teams available for children with spina bifida are generally lacking or inconsistent for adults,[28] leading to a greater use of emergency services for adult care.[32] Coordinated, patient-centered programs are emerging that engage the individual, family, persons in the school and workplace, and health care providers and allied health services in a staged approach years before the transfer of care to adult medical services is needed.[33,34] This approach is prioritized by advocacy organizations, patients, and families.

FUTURE DIRECTIONS

Emerging technologies, such as enhanced neuroendoscopy, intraoperative surgical image guidance, augmented reality–assisted surgery, and new shunt designs, may improve neurologic outcomes but have not yet been systematically evaluated.[35] Future improvements in fetal surgery may include robotic applications for precise and efficient repairs,[36] tissue engineering to facilitate watertight dural closure,[37] and stem-cell technology to attempt earlier spina bifida repairs,[38] each based on preliminary experiments in animals. Bladder neurostimulation may play a

role in improving continence,[39] and investigation of remotely controlled magnetic rods instead of spinal fusion to treat scoliosis in growing children has provided preliminary evidence for use in children with spina bifida.[40] Global accessibility to care is still lacking,[41] and the neurosurgical community in high-income countries is partnering with neurosurgical centers elsewhere to provide in-person training, telecollaboration, and augmented reality tools for the use of modern endoscopic and surgical techniques.[42]

Rigorous study of folate supplementation and food fortification protocols to determine favorable folate compounds, doses, and frequency and timing of administration; serial testing to achieve target levels of folate; and preventive measures tailored to the needs of each country or region on the basis of epidemiologic data could all help to prevent spina bifida.

CONCLUSIONS

Prevention and management of spina bifida have benefited from public health policy, modern surgical and imaging technology, and multidisciplinary approaches in partnership with the patient, family, and advocacy groups. Surgical correction of the defect is coupled with comprehensive care to achieve good clinical results and quality of life for affected patients as they progress from childhood to adulthood.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Joyce Koueik for assistance in background research and Kirk Hogan, Brittany Allen, David Joseph, Jacqueline Parchem, Brady Lundin, Randolph Ashton, John (Jay) Wellons, Abhaya Kulkarni, Catherine Mazzola, and the University of Wisconsin Pediatric Spina Bifida Clinic providers (Blaise Nemeth, Kenneth Noonan, Ruthie Su, Walid Farhat, Lisa McLennan, James [Andy] Stadler, Raheel Ahmed, and Melissa Villejas) for advice or critical comments on an earlier version of the manuscript.

REFERENCES

1. Wolujewicz P, Steele JW, Kaltschmidt JA, Finnell RH, Ross ME. Unraveling the complex genetics of neural tube defects: from biological models to human genomics and back. Genesis 2021;59(11):e23459.
2. Botto LD, Moore CA, Khoury MJ, Erickson JD. Neural-tube defects. N Engl J Med 1999;341:1509-19.
3. Shoja MM, Tubbs RS, Oakes WJ. Embryology and pathophysiology of the Chiari I and II malformations. In: Tubbs RS, Turgut M, Oakes WJ, eds. The Chiari malformations. 2nd ed. New York: Springer Nature Switzerland, 2020:87-108.
4. McLone DG, Knepper PA. The cause of Chiari II malformation: a unified theory. Pediatr Neurosci 1989;15:1-12.
5. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991;338:131-7.
6. Grosse SD, Collins JS. Folic acid supplementation and neural tube defect recurrence prevention. Birth Defects Res A Clin Mol Teratol 2007;79:737-42.
7. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR Recomm Rep 1992;41:1-7.
8. Centers for Disease Control and Prevention (CDC). Spina bifida and anencephaly before and after folic acid mandate — United States, 1995–1996 and 1999–2000. MMWR Morb Mortal Wkly Rep 2004;53:362-5.
9. Atta CAM, Fiest KM, Frolkis AD, et al. Global birth prevalence of spina bifida by folic acid fortification status: a systematic review and meta-analysis. Am J Public Health 2016;106(1):e24-e34.
10. Kancherla V, Wagh K, Pachón H, Oakley GP Jr. A 2019 global update on folic acid — preventable spina bifida and anencephaly. Birth Defects Res 2021;113:77-89.
11. Ross ME, Mason CE, Finnell RH. Genomic approaches to the assessment of human spina bifida risk. Birth Defects Res 2017;109:120-8.
12. Copp AJ, Adzick NS, Chitty LS, Fletcher JM, Holmbeck GN, Shaw GM. Spina bifida. Nat Rev Dis Primers 2015;1:15007.
13. Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. Folate levels and neural tube defects. Implications for prevention. JAMA 1995;274:1698-702.
14. Crider KS, Devine O, Hao L, et al. Population red blood cell folate concentrations for prevention of neural tube defects: Bayesian model. BMJ 2014;349:g4554.
15. Mazzola CA, Assassi N, Baird LC, et al. Congress of Neurological Surgeons systematic review and evidence-based guidelines for pediatric myelomeningocele: executive summary. Neurosurgery 2019;85:299-301.
16. Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 2011;364:993-1004.
17. Goodnight WH, Bahtiyar O, Bennett KA, et al. Subsequent pregnancy outcomes after open maternal-fetal surgery for myelomeningocele. Am J Obstet Gynecol 2019;220(5):494.e1-494.e7.
18. Bennett KA, Carroll MA, Shannon CN, et al. Reducing perinatal complications and preterm delivery for patients undergoing in utero closure of fetal myelomeningocele: further modifications to the multidisciplinary surgical technique. J Neurosurg Pediatr 2014;14:108-14.
19. Houtrow AJ, MacPherson C, Jackson-Coty J, et al. Prenatal repair and physical functioning among children with myelomeningocele: a secondary analysis of a randomized clinical trial. JAMA Pediatr 2021;175(4):e205674.
20. Sanz Cortes M, Chmait RH, Lapa DA, et al. Experience of 300 cases of prenatal fetoscopic open spina bifida repair: report of the International Fetoscopic Neural Tube Defect Repair Consortium. Am J Obstet Gynecol 2021;225(6):678.e1-678.e11.
21. Al-Hakim S, Schaumann A, Schneider J, Schulz M, Thomale U-W. Experience in shunt management on revision free survival in infants with myelomeningocele. Childs Nerv Syst 2018;34:1375-82.
22. Drake JM, Kestle JR, Milner R, et al. Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. Neurosurgery 1998;43:294-303.
23. Riva-Cambrin J, Kestle JRW, Holubkov R, et al. Risk factors for shunt malfunction in pediatric hydrocephalus: a multicenter prospective cohort study. J Neurosurg Pediatr 2016;17:382-90.
24. Warf BC, Campbell JW. Combined endoscopic third ventriculostomy and choroid plexus cauterization as primary treatment of hydrocephalus for infants with myelomeningocele: long-term results of a prospective intent-to-treat study in 115 East African infants. J Neurosurg Pediatr 2008;2:310-6.
25. Iskandar BJ, McLaughlin C, Mapstone TB, Grabb PA, Oakes WJ. Pitfalls in the

diagnosis of ventricular shunt dysfunction: radiology reports and ventricular size. Pediatrics 1998;101:1031-6.
26. Reynolds RA, Ahluwalia R, Krishnan V, et al. Risk factors for unchanged ventricles during pediatric shunt malfunction. J Neurosurg Pediatr 2021 September 24 (Epub ahead of print).
27. Oakes WJ. Treatment of the Chiari II malformation. In: Tubbs RS, Turgut M, Oakes WJ, eds. The Chiari malformations. 2nd ed. New York: Springer Nature Switzerland, 2020:459-64.
28. Guidelines for the care of people with spina bifida. 4th ed. Arlington, VA: Spina Bifida Association. 2018 (https://www.spinabifidaassociation.org/wp-content/uploads/Guidelines-for-the-Care-of-People-with-Spina-Bifida-2018.pdf).
29. Snow-Lisy DC, Yerkes EB, Cheng EY. Update on urological management of spina bifida from prenatal diagnosis to adulthood. J Urol 2015;194:288-96.
30. Kroll P. The current role of Botox in a pediatric neurogenic bladder condition. Curr Bladder Dysfunct Rep 2019;14:115-23.
31. Park JS, Lee YS, Lee CN, Kim SH, Kim SW, Han SW. Efficacy and safety of mirabegron, a β3-adrenoceptor agonist, for treating neurogenic bladder in pediatric patients with spina bifida: a retrospective pilot study. World J Urol 2019;37:1665-70.
32. Domino JS, Lundy P, Glynn EF, Partington M. Estimating the prevalence of neurosurgical interventions in adults with spina bifida using the Health Facts data set: implications for transition planning and the development of adult clinics. J Neurosurg Pediatr 2021;29:371-8.
33. Hopson B, Alford EN, Zimmerman K, Blount JP, Rocque BG. Development of an evidence-based individualized transition plan for spina bifida. Neurosurg Focus 2019;47(4):E17.
34. Le JT, Mukherjee S. Transition to adult care for patients with spina bifida. Phys Med Rehabil Clin N Am 2015;26:29-38.
35. Lutz BR, Venkataraman P, Browd SR. New and improved ways to treat hydrocephalus: pursuit of a smart shunt. Surg Neurol Int 2013;4:Suppl 1:S38-S50.
36. Diana M, Marescaux J. Robotic surgery. Br J Surg 2015;102(2):e15-e28.
37. Pedreira DAL, Zanon N, Nishikuni K, et al. Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. Am J Obstet Gynecol 2016;214(1):111.e1-111.e11.
38. Bardill J, Williams SM, Shabeka U, Niswander L, Park D, Marwan AI. An injectable reverse thermal gel for minimally invasive coverage of mouse myelomeningocele. J Surg Res 2019;235:227-36.
39. Choi EK, Hong CH, Kim MJ, Im YJ, Jung HJ, Han SW. Effects of intravesical electrical stimulation therapy on urodynamic patterns for children with spina bifida: a 10-year experience. J Pediatr Urol 2013;9:798-803.
40. Johari AN, Nemade AS. Growing spine deformities: are magnetic rods the final answer? World J Orthop 2017;8:295-300.
41. Meara JG, Leather AJM, Hagander L, et al. Global surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Surgery 2015;158:3-6.
42. Haji FA, Lepard JR, Davis MC, et al. A model for global surgical training and capacity development: the Children's of Alabama–Viet Nam pediatric neurosurgery partnership. Childs Nerv Syst 2021;37:627-36.

Supplementary Appendix

Supplement to: Iskandar BJ, Finnell RH. Spina bifida. N Engl J Med 2022;387:444-50. DOI: 10.1056/NEJMra2116032

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Supplement to: Iskandar BJ, Finnell RH. Spina Bifida

Contents

Table S1: Issues that affect the quality of life of individuals with spina bifida

Issues	Goals	Challenges
Hydrocephalus ○ Enlarged cerebral ventricles with increased ICP ○ Treatment delays may lead to neuro-cognitive compromise and death	○ Preserve neuro-cognitive function ○ Decrease reliance on shunts ○ Decrease morbidity and death from shunt malfunction and shunt surgery	○ Prenatal myelomeningocele repair leads to a decrease in incidence of hydrocephalus, but not its elimination ○ Shunts continue to have high malfunction rates despite improvement in technology ○ Shunt malfunction may not be evident on imaging, thus causing diagnostic difficulties and potential morbidity and death ○ No commercial shunt valve has shown superiority in shunt malfunction rates ○ ETV/CPC is not as effective in older children and adults as in infants ○ The efficacy of ETV/CPC in African infants awaits replication in multi-center North American clinical trials
Chiari II Malformation ○ Herniation of hindbrain structures (vermis and medulla) into the cervical spine ○ Associated with lower brainstem dysfunction	○ Recognize and address symptoms of lower brainstem dysfunction (e.g., stridor, vocal cord paralysis, dysphagia, apnea) ○ Surgical decompression of Chiari II is rarely needed ○ Chiari II symptoms most often related to shunt malfunction	○ Prenatal myelomeningocele repair leads to a decrease in incidence of Chiari II, but not its elimination
Tethered cord syndrome ○ Caused by postoperative scar tissue that tether the repaired spinal placode to the surrounding dura ○ To be distinguished from the congenital TCS in spina bifida occulta patients who are born with congenital anomalies that tether the spinal cord, such as a thickened filum terminale, split cord malformation, dermal sinus tract, and lipomyelomeningocele ○ Clinical presentation includes back and leg pain, worsening lower extremity sensorimotor function, deterioration in bowel and bladder function, and progressive scoliosis	○ Address progressive symptomatology with surgical tethered cord release	○ TCS is a clinical diagnosis. Imaging is not as useful at recognizing TCS, because most repaired myelomeningoceles appear tethered on MRI, even if asymptomatic and don't warrant surgery ○ Surgical correction of a tethered spinal cord faces the technical challenge of separating spinal tissues from surrounding adhesions without functional compromise ○ Effectiveness of intraoperative neuromonitoring has not been verified in large studies ○ Tethered cord release often leads to recurrent adhesions requiring repeat surgery

Issues	Goals	Challenges
Syringomyelia ○ Cystic cavitation of the spinal cord ○ Can be caused by hydrocephalus (shunt malfunction), Chiari II, or spinal cord tethering ○ Can extend into the brainstem (syringobulbia) ○ Presents with sensorimotor dysfunction in trunk and extremities	○ Treat the offending etiology (shunt malfunction, tethered cord syndrome) ○ Avoid direct syrinx drainage if possible (associated with complications and not effective long-term)	○ Determining the etiology of a syrinx in spina bifida patients is often challenging
Musculoskeletal function* ○ Kyphoscoliosis ○ Limb deformities ○ Hip subluxation/dislocation ○ Decreased mobility	○ Achieve a stable and balanced spine ○ Optimize pulmonary function ○ Identify, stabilize, or correct lower limb deformities early ○ Preserve or improve gait efficiency	○ Optimal timing of orthopedic surgery is still controversial ○ Optimal timing and frequency of screening radiography are still controversial
Urogenital function* ○ Incontinence ○ Urinary tract infections ○ Upper urinary tract damage from poorly managed bladder function ○ Sexual dysfunction and dissatisfaction	○ Maintain normal renal function ○ Prevent UTIs ○ Develop strategies for urinary continence ○ Achieve independence with personal care	○ Definition and treatment of incontinence at different centers are widely variable ○ Definition and treatment of UTI is widely variable, particularly in the setting of intermittent catheterization ○ Timing of bladder reconstructive or diversion surgery is still controversial
Bowel function* ○ Bowel incontinence (most important issue in children according to 50% of parents) ○ Constipation	○ Promote healthy bowel habits ○ Decrease bowel incontinence ○ Specific goals: monitor stool frequency, consistency and amount; dietary management; oral and rectal pharmacologic adjuncts; barrier creams; education and behavioral interventions	○ Research into efficacy of bowel regimens is hindered by variability in clinical practice and non-standardized definitions of bowel success
Skin* Pressure ulcers in insensate regions	○ Teach parents and caregivers to inspect skin ○ Use barrier creams ○ Check bath water temperature ○ Ensure well-fitting orthoses	○ Management strategies to care for insensate skin need development ○ Strategies to reduce incidence of skin breakdown need development

Issues	Goals	Challenges
Latex allergy* ○ >50% of persons with spina bifida	○ Increase awareness of latex allergy ○ Avoid direct contact to natural rubber latex and latex-containing products in all people with spina bifida ○ Some spina bifida individuals develop an allergy to proteins in some fruits, known as the “latex fruit syndrome”	○ Recognizing individuals most at risk remains challenging ○ Awareness about latex allergy is still limited ○ Consensus on diagnosis and timing of latex allergy is needed
Skin* ○ Pressure ulcers in insensate regions	○ Teach parents and caregivers to inspect skin ○ Use barrier creams to protect skin from damage related to bowel and bladder incontinence ○ Check bath water temperature ○ Ensure well-fitting orthoses	○ Management strategies to care for insensate skin need development ○ Strategies to reduce incidence of skin breakdown need development
Nutrition and obesity* ○ Increased prevalence because of decreased mobility, brainstem dysfunction with dysphagia, bowel dysfunction, and psychosocial issues such as repetitive hospitalization and home stress	○ Promote wellness and healthy nutrition ○ Promote mobility and an active lifestyle ○ Manage constipation	○ Adults and families from lower socioeconomic households may have food insecurity ○ Improving mobility in spina bifida individuals can be challenging ○ Evidence-based guidelines for weight-management, obesity prevention, and obesity treatment specific to children and adults with Spina Bifida are needed ○ Growth curves and weight classification cut-offs specifically for children and adults with Spina Bifida need to be developed
Sleep-related breathing disorders (SRBD) * ○ Affects the majority of individuals with spina bifida ○ Central and peripheral apnea ○ May cause unexplained death	○ Discuss SRBD with parents and care providers so they can better observe for early symptoms or changes ○ Improve patient awareness of SRBD, its presentation and its adverse impact on quality of life ○ Encourage the use of overnight polysomnography in all individuals with spina bifida	○ Clinical evaluation of SRBD and overnight pulse oximetry have low sensitivity ○ Clinical evaluation cannot distinguish between asymptomatic individuals from those who have sub-clinical SRBD ○ Screening cardiorespiratory protocols are needed based on age and lesion level

Issues	Goals	Challenges
Cognition and mental health* ○ Score below average on neuropsychological functioning, depression and anxiety measures	○ Screen for depression or anxiety ○ Encourage activities and hobbies that improve face-to-face social contact ○ Refer for social skills training as needed ○ Assess for at-risk behaviors ○ Build on resources that encourage resilience	○ Age-based mental health support guidelines should be optimized
Quality of life measures* ○ Score below average on social and emotional maturity, dependence and participation in daily living	○ Use a systematic approach to evaluating QOL/HRQOL. ○ Encourage independence, praise for accomplishment, and provide opportunities for fun ○ Target areas that affect quality of life, including continence, pain, and psychosocial health	○ Research that examines best practices for children with spina bifida that influence transition is needed ○ Age-based guidelines to enhance future independence and employment ability should be developed ○ Efforts to train adult specialists in the care of the spina bifida patient are needed

***** Summarized with permission from the Spina Bifida Association Guidelines.[1,2]

References

1. Guidelines for the care of people with spina bifida. 4th ed: Spina Bifida Association; 2018:1-247.
2. Guidelines for the care of people with spina bifida (themed issue). J Pediatr Rehabil Med 2020;13(4).