Open Neural Tube Defects

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Neural tube defects (NTDs) are malformations of the brain, spinal cord, or both that originate during embryonic development when the neural tube fails to close completely.

Classification

Terminology and classification systems surrounding NTDs have been varied, often leading to confusion. Figure 1 presents a simple classification scheme for NTDs, as described below.

Broadly, neural tube defects can be classified as *open*, where neural tissue is exposed to the surface, or *closed*, where the defect is covered by skin; open defects arise during neurulation, and closed defects arise thereafter (Lemire 1988).

As described in a later section of this chapter, NTDs include defects that arise from improper folding and fusion of the neural tube (i.e., *craniorachischisis*), failure of closure of the anterior neuropore (i.e., *anencephaly*), and failure of closure of the posterior neuropore (i.e., *spina bifida*) (Lemire 1988). In anencephaly, there is complete or partial absence of the brain and calvarium. Craniorachischisis is characterized by anencephaly accompanied by a contiguous bony defect in the spine, resulting in exposure of both the brain and spinal cord to the external environment. Anencephaly and craniorachischisis are incompatible with life; such cases end in spontaneous abortion in pregnancy or death shortly after birth (Jaquier et al. 2006; Creasy and Alberman 1976; Melnick and Myrianthopoulos 1987; McLean 1987; Obeidi et al. 2010). *Iniencephaly* results from failure of fusion of the occipital portion of the cranium and upper spine; there is associated severe retroflexion of the neck and trunk. There have been case reports of long-term survival with iniencephaly (Aytar et al. 2007; Gartman et al. 1991). *Cephalocele* refers to protrusion of the brain (i.e., *encephalocele*) or meninges (i.e., *cranial meningocele*) through a defect in the cranium.

Spina bifida or *spinal dysraphism* are broad terms that encompass all defects arising from improper closure of the posterior neuropore; these are characterized by a bony defect in the

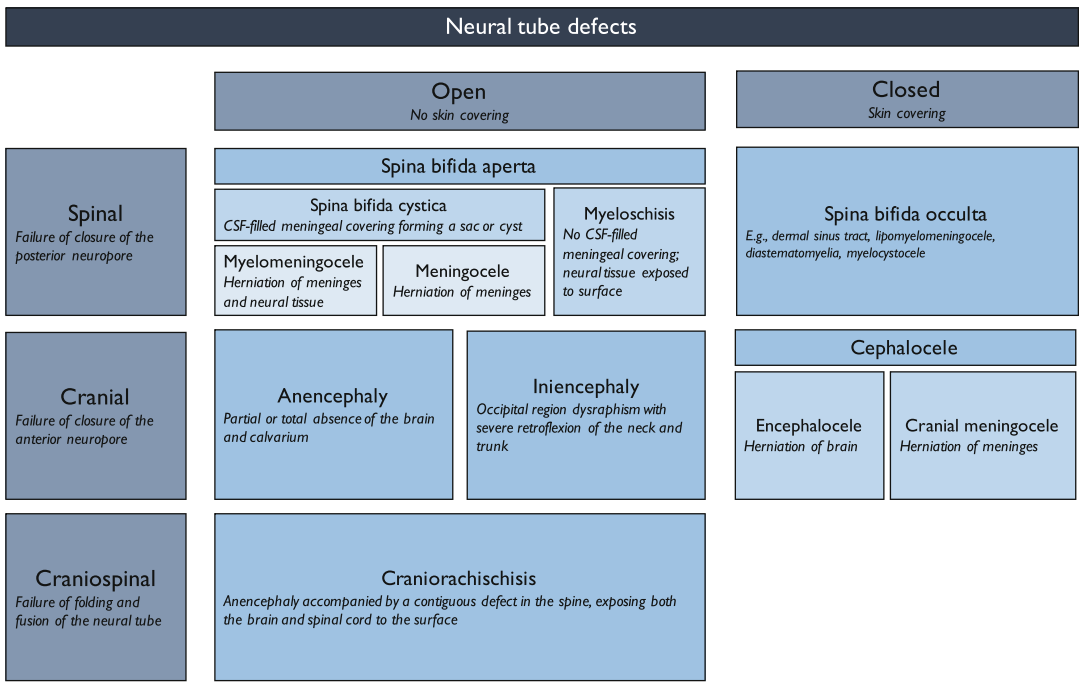

Fig. 1 Classification of neural tube defects

posterior vertebral arches. In *spina bifida aperta* or *open spina bifida*, a dermal covering is lacking, and the midline lesion is exposed to the external environment. *Spina bifida cystica* is a subtype of spina bifida aperta wherein the lesion is contained within a meningeal lining that forms a CSF-filled sac or "cyst"; if there is only herniation of meninges through the spinal defect, this is a *meningocele*, and if there is herniation of both meninges and neural elements, it is termed a *myelomeningocele*. In myelomeningocele, the spinal cord does not fuse dorsally during primary neurulation, resulting in a flat plate of neural tissue termed the *neural placode*. *Myeloschisis* essentially refers to myelomeningocele without a CSF-filled cystic covering.

Spina bifida occulta or *closed spina bifida* are skin-covered lesions that may lead to neurological deterioration by tethering the spinal cord. Because such lesions are not immediately visible externally, their diagnosis often hinges upon the astute clinician's recognition of cutaneous, orthopedic, urological, or neurological stigmata of an occult spinal dysraphism, which may include a "hairy patch" (hypertrichosis), sacral dimple, dermal sinus tract, subcutaneous lipoma, hemangioma, leg-length discrepancy, foot deformity, neurogenic bladder, frequent urinary tract infections, upper or lower motor neuron signs, gait difficulty, or sensory changes (Bui et al. 2007; Lew and Kothbauer 2007).

Herein, for simplicity, "NTDs" refers to anencephaly or spina bifida, and spina bifida refers to open spina bifida.

Epidemiology

The prevalence of open NTDs has declined over the past several decades owing to prenatal diagnosis and elective termination of affected pregnancies and folic acid supplementation. In the United States, rates of NTDs fell from 1.3 per 1,000 births in 1970 to 0.6 per 1,000 births in 1989 (Yen et al. 1992). Over the same interval, the relative proportion of spina bifida versus anencephaly cases increased (Yen et al. 1992). From 1983 to 1990, the prevalence of spina bifida in the United States was 0.46 cases per 1,000 births (Lary and Edmonds 1996). The incidence of spina bifida declined by 7.8% annually from 1983 to 1990, from a peak of 0.59 cases per 1,000 births in 1984 to 0.32 cases per 1,000 births in 1990 (Lary and Edmonds 1996). Much of the drop in the prevalence of NTDs is attributed to prenatal diagnosis (Lary and Edmonds 1996). Cragan et al. found from 1985 to 1994 in some areas of the United States, prenatal diagnosis and subsequent termination of pregnancy reduced the birth prevalence of anencephaly by 60–70% and that of spina bifida by 20–30% (Cragan et al. 1995). Nonetheless, the fact that this decline began before widespread adoption of prenatal diagnostic techniques in the mid-1980s suggests a role for environmental factors, such as maternal nutrition, in the etiology of NTDs (Yen et al. 1992; Lary and Edmonds 1996).

In 1992, the US Public Health Service recommended that all women capable of becoming pregnant consume 0.4 mg of folate daily. However, a 1998 survey found only 29% of US women were meeting the recommended intake and only 7% knew folic acid should be taken before pregnancy to reduce the risk of NTDs (Centers for Disease Control and Prevention (CDC) 1999). Mandatory fortification of cereal grain products with 140 μg of folic acid per 100 g of grain began in January 1998 (Food and Drug Administration 1996). Williams et al. found the prevalence of spina bifida and anencephaly decreased by 31% and 16%, respectively, following folic acid supplementation (Williams et al. 2002). There was a 19% reduction in the birth prevalence of NTDs comparing rates before and after folic acid fortification (Honein et al. 2001). Similarly, the Centers for Disease Control and Prevention (CDC) reported the number of NTD-affected pregnancies decreased by 27% from 1995–1996 to 1999–2000, representing prevention of approximately 1,000 cases annually (Centers for Disease Control and Prevention (CDC) 2004). A recent study evaluating the birth prevalence of NTDs from 1995 to 2011 found the prevalence of anencephaly and spina bifida has been stable since these initial reductions (Williams et al. 2015).

There is significant geographic and racial variation in the prevalence of NTDs. The highest rates have been reported in the United Kingdom, particularly Ireland and Wales, where even today the incidence exceeds 1 per 1,000 births (McDonnell et al. 2015). A recent population-based study evaluating neural tube defect cases from 1991 to 2011 found a prevalence of 1.5 1,000 births in Wales, 0.5 per 1,000 births in Italy, and 0.9 per 1,000 in Finland and Norway; overall, the pooled total prevalence of neural tube defects in 19 European countries was 0.91 per 1,000 births (Khoshnood et al. 2015). This is compared to 0.7 per 1,000 in the United States (Williams et al. 2015). Within the United States, the prevalence of NTDs is highest among Hispanics and lowest among Asians. In a US study where the overall prevalence of spina bifida was 0.46 per 1,000 births, the prevalence per 1,000 births was 0.6 among Hispanics, 0.5 among American Indians, 0.45 among whites, 0.37 among blacks, and 0.23 among Asians (Lary and Edmonds 1996). On an international level, the prevalence of spina bifida varies widely from 0.1 per 1,000 among native Africans to 12.5 per 1,000 among Celts (Shurtleff and Lemire 1995). Interestingly, the pattern and severity of the defect also varies with ethnicity. Thoracic lesions with high motor function and severe cognitive impairment are common among Celts, whereas thoracic lesions also occur among the Sikhs in western Canada, but these patients tend to generally have good motor function (Shurtleff and Lemire 1995).

The burden of disease of open NTDs is high. Each year in the United States, 3,000 fetuses are affected by spina bifida or anencephaly, and nearly one third of these are lost by either spontaneous or elective abortion (Centers for Disease Control and Prevention (CDC) 2004). Anencephaly is uniformly fatal, whereas open spina bifida often portends considerable lifelong physical and psychosocial disability, the severity of which likely depends on the rostral-caudal level of the lesion, extent of the original neurological deficit, presence of hydrocephalus, and CSF shunt-related morbidity (Oakeshott and Hunt 2003; Date et al. 1993; Hunt and Poulton 1995; Oakeshott et al. 2012; Holmbeck and Faier-Routman 1995; Zurmöhle et al. 1998). The economic costs of NTDs are also staggering. The lifetime direct costs for a child with spina bifida are estimated at $560,000 (Grosse et al. 2008).

Pathogenesis/Embryology

Normal development of the nervous system is discussed in detail elsewhere. Formation of the central nervous system (CNS) begins during the third week of embryonic life when the neural plate forms as a thickening of the dorsal surface ectoderm (Sadler 2005; Copp and de Greene 2009). The lateral edges of the neural plate become elevated to form the neural folds, which eventually move toward the midline and fuse to form the neural tube. According to traditional theory, the fusion begins in the cervical region and proceeds rostrally and caudally, resulting in closure of the anterior neuropore on day 25 and posterior neuropore on day 28. More recently, there has been evidence to suggest neural tube closure is initiated at multiple points along the body axis (Copp and de Greene 2009; Copp et al. 2013; Golden and Chernoff 1993). The most extensively studied has been the rodent model, where fusion begins at the junction between the hindbrain and spinal cord (closure 1). Additional closure sites begin at the midbrain-forebrain boundary (closure 2) and at the rostral extent of the forebrain (closure 3). The result is three regions of open neural folds between the sites of initial closure (neuropores) that close progressively as fusion proceeds in a zipper-like fashion bidirectionally from sites of closure 1 and 2 and caudally from site of closure 3. The anterior and hindbrain neuropores complete closure first, followed by the posterior neuropore, marking the end of primary neurulation. Though it is debated, in humans, closure 2 probably does not exist, and hence there remains a single rostral neuropore (Copp et al. 2013; O'Rahilly and Müller 2002).

As discussed previously, failure of closure of the neural tube produces an open NTD, and the site of non-closure determines the type of defect. Craniorachischisis results from failure of closure 1 (Copp et al. 1994). However, most embryos that

develop NTDs fail later during neurulation, presenting with open defects of the rostral neuropore (i.e., anencephaly) or caudal neuropore (i.e., open spina bifida) (Copp et al. 2013). The zippering closure of the neural tube may arrest at any point, and for any length, along the neuraxis, producing open defects of varying sizes at varying levels.

Another theory of the etiology of NTDs suggests these defects result not from failure of the neural tube to close but rather from its overdistention and eventual rupture following closure (Gardner 1980). The "overdistention theory," however, has fallen out of favor, as experimental evidence has substantiated the "non-closure theory."

McLone proposed a unified theory for the development of Chiari II malformation in children with myelomeningocele (McLone and Knepper 1989). After closure of the anterior neuropore, the neurocele (embryonic central canal of the spinal cord) communicates with the amniotic fluid via the posterior neuropore. Prior to closure of the posterior neuropore, the neurocele occludes transiently, a process known as *occlusion*. The result is that the cranial vesicles are isolated from the amniotic fluid, which prevents drainage of fluid from the vesicles and maintains them in a distended state. Once the posterior neuropore has closed, the neurocele reopens, and no fluid is lost from the cranial vesicles. The pressure within the cranial vesicles is increased compared to that of the amniotic fluid, and this is critical to normal brain growth and development (Desmond and Jacobson 1977; Desmond 1985). When the neural tube fails to close prior to reopening of the neurocele, CSF egress from the defect prevents the accumulation of fluid and pressure within the cranial vesicles. The lack of distention results in malformation of the cranium, including a small posterior fossa. As the cerebellum and brainstem then develop, they extrude inferiorly into the spinal canal and upward into the middle fossa; that is, there is both downward and upward herniation. Other abnormalities of the cranium and its contents include lückenschädel, abnormal gyri of the cerebral hemispheres, cerebellar dysplasia, colpocephaly, tectal beaking, and cervicomedullary kinking, among others.

Etiology

The etiology of NTDs is multifactorial, with both genetic and environmental contributions. The wide geographic and racial variation in the prevalence of NTDs likely reflects differential contributions of risk factors, such as nutritional status, use of folic acid supplementation, and exposure to environmental toxins, superimposed on differing genetic predisposition among various populations (Greene and Copp 2014). Despite the number of risk factors identified, these may account for less than half of NTDs, indicating that additional genetic and nongenetic factors remain to be identified (Table 1) (Agopian et al. 2013).

Gender

Anencephaly is more prevalent among females than males (Little and Elwood 1980; Elwood et al. 1992). A female gender predisposition for cranial NTDs has also been observed in mouse models, apparently reflecting greater sensitivity of the female embryo to disturbance of cranial neural tube closure (Juriloff and Harris 2012).

Folate

Hibbard and Smithells suspected the association between folate deficiency and NTDs in the 1960s (Hibbard and Smithells 1965; Hibbard 1964). Lower blood folate levels were observed in mothers of NTD fetuses (Smithells et al. 1976). This prompted Smithells and colleagues to organize an intervention trial of folic acid-containing multivitamin supplementation (0.36 mg folic acid daily) among women with a prior history of an NTD-affected pregnancy. Recurrence of NTD was observed in 4% of unsupplemented versus 0.5% of supplemented mothers (Smithells et al. 1981). However, it was unclear from this study whether folic acid or one of the other seven vitamins contained in the multivitamin produced the observed treatment effect. Moreover, this study followed a non-randomized design, and hence there was the possibility of selection bias, in that

Table 1 Adjusted attributable risk estimates for established NTD risk factors

Variable	Risk (%)		
	Spina bifida	Anencephaly	Spina bifida and anencephaly
Female infant sex	1.1	8.7	3.3
Family history	1.8	2.2	1.9
Hispanic ethnicity	8.1	15.2	9.9
Obesity	9.9	2.2	7.1
No folic acid supplementation	1.8	4.5	2.6
Low dietary folate intake	4.2	10.0	5.7
Anticonvulsant use	0.9	0.6	0.8
Pregestational diabetes		0.4	
Gestational diabetes			
Hot tub or sauna use		0.4	
Combined	*27.6*	*44.4*	*31.1*

Adopted from (Agopian et al. 2013)

women who chose to take the multivitamin may have represented a more health conscious group, with a healthier diet, and lower risk of having a further affected pregnancy (Wald 2011). A subsequent multicenter randomized controlled trial, the MRC Vitamin Study, resolved these issues. One thousand, eight hundred seventeen women with a previous NTD-affected pregnancy were randomized to 1 of 4 groups – supplementation with folic acid (4 mg daily), other vitamins (A, D, B1, B2, B6, C, and nicotinamide), both, or neither. Folic acid supplementation demonstrated a 72% protective effect against NTDs, whereas the other vitamins showed no significant protective effect (MRC Vitamin Study Research Group 1991). Other clinical trials reinforced reduction in risk of NTDs with folic acid supplementation (Czeizel and Dudás 1992; Czeizel et al. 2011; Berry et al. 1999).

Clinical guidelines and recommendations for folic acid supplementation in pregnancy are provided by a number of organizations, including the US Public Health Service, US Preventive Services Task Force (USPSTF), American Academy of Family Physicians (AAFP), American College of Obstetrics and Gynecology (ACOG), and American Academy of Neurology (AAN) (ACOG Committee on Practice Bulletins 2003; American Academy of Family Physicians (AAFP) 2017; U.S. Preventive Services Task Force 2009; American Academy of Neurology 1998; American Academy of Pediatrics Committee on Genetics 1999). Current guidelines recommend all women planning pregnancy take 0.4–0.8 mg of folic acid daily beginning 1 month prior to conception and continuing throughout the first trimester; all women capable of pregnancy take 0.4 mg of folic acid daily to reduce the risk of NTDs in unplanned pregnancies; and women who have had a previous NTD-affected pregnancy take 4 mg of folic acid daily. Other women at high risk, including those with a partner with NTD, a close relative with NTD, type I diabetes mellitus, seizure disorder treated with valproic acid or carbamazepine, mutations in folate-related enzymes, or obesity, may be advised to take 4 mg of folic acid daily. Importantly, women should not attempt to achieve the 4 mg daily dosage of folic acid by taking multivitamins, because of the possibility of reaching toxic levels of other vitamins, particularly vitamin A (Lewis et al. 1998a).

Folate is a B vitamin and natural compound in food. Folic acid is synthetic form of folate with greater bioavailability than folate in food (Winkels et al. 2007). Folate breakdown is accelerated in pregnancy, and several factors may decrease folate absorption and bioavailability, including cigarette smoking and use of oral contraceptives (McPartlin et al. 1993; Piyathilake et al. 1994; Lewis et al. 1998b). Multiple anticonvulsants may also reduce folate levels (Morrell 2002). Fortification of cereal grain products in

the United States is estimated to provide 0.1–0.2 mg of folic acid per day (Crider et al. 2011). There has been uncertainty about possible unintended consequences of folic acid fortification, and there few risks to excess folate. Folate may mask a vitamin B_{12} deficiency. Moreover, it may lower the seizure threshold, although folic acid in physiologic concentrations does not promote seizures (Morrell 2002). Several studies have favored folate fortification as a cost-effective public health intervention (Bentley et al. 2009; Jentink et al. 2008; Postma et al. 2002).

The mechanism by which folic acid promotes neural tube closure remains an area of investigation. Folate enters one-carbon metabolism, which has two primary roles: (1) production of purines and pyrimidines for DNA synthesis and (2) donation of methyl groups to macromolecules, including DNA, proteins, and lipids (Copp et al. 2013). Cell proliferation is critical to the process of neural tube closure. Hence, one hypothesis is that a deficiency of folic acid results in an inadequate supply of nucleotides; as a result, cell replication, and consequently, development of the neural folds, is slowed (Copp et al. 1988; Smith and Schoenwolf 1987; Barber et al. 1999). There is data from animal studies to support this hypothesis. In the splotch (*Pax3*) mouse model, folate deficiency worsens cranial NTDs. These mice exhibit deficient deoxythymidine monophosphate (dTMP) biosynthesis. Supplementation with exogenous thymidine or folic acid can rescue NTDs, suggesting that folic acid may prevent NTDs by supporting de novo thymidine biosynthesis (Barber et al. 1999; Fleming and Copp 1998; Imbard et al. 2013).

The role of folic acid in methylation may also mediate its impact on NTDs. Methyltetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism and generates 5-methyltetrahydrofolate (5-MeTHF). Methionine synthase uses 5-MeTHF as a methyl donor to remethylate homocysteine, producing methionine. This enzyme requires vitamin B12 as a cofactor. Methionine is then converted to *S*-adenosylmethionine, which is the most ubiquitous methyl donor in mammals, serving as the substrate for methylation of nucleic acids, proteins, and lipids. Transfer of the methyl group converts *S*-adenosylmethionine to *S*-adenosylhomocysteine, which is subsequently hydrolyzed to adenosine and homocysteine (Barber et al. 1999; Imbard et al. 2013). Studies have linked homocysteine metabolism to NTDs. Mills et al. found significantly higher homocysteine levels in women with a previous NTD-affected pregnancy compared to control mothers (Mills et al. 1995, 1996). A deficiency in MTHFR or methionine synthase activity would lead to high levels of homocysteine, low levels of methionine, and, in turn, low levels of *S*-adenosylmethionine and ultimately reduced methylation within several critical intracellular processes. Furthermore, the accumulation of homocysteine causes the equilibrium of the S-adenosylhomocysteine reaction to favor and lead to a buildup of S-adenosylhomocysteine, which is a potent inhibitor of methyltransferases (Imbard et al. 2013). Indeed, genetic mutations in MTHFR have been associated with NTDs. The *MTHFR* 677C → T polymorphism is associated with a 1.6-fold greater risk of giving birth to an infant with an NTD in homozygous mothers and 1.9-fold greater risk of being born with an NTD in homozygous offspring (Blom et al. 2006).

While the prevalence of NTDs in the United States has been stable over the past decade or so, there remain opportunities for further prevention of NTDs, and recent reports have reinforced the importance of folic acid supplements (Centers for Disease Control and Prevention (CDC) 2013, 2015). Mandatory folic acid fortification in the United States has decreased the prevalence of serum folate deficiency (<10 nmol/L) from 24% to 0.7% and RBC folate deficiency (<340 nmol/L) from 3.5% to 0.1% (Pfeiffer et al. 2012). Fewer Hispanic women (17%) than non-Hispanic white women (30%) report consuming >0.4 mg of folic acid daily through supplements or fortified foods (Tinker et al. 2010). However, the *MTHFR* 677C → T polymorphism is very common among Hispanics, and hence this population may be particularly susceptible to folate insufficiency and resultant NTDs (Botto and Yang 2000). Studies in the Mediterranean Spanish population, as well as in Hispanic populations of California and Colombia, have reported this polymorphism to

occur in nearly 25% of individuals (Botto and Yang 2000; Guillén et al. 2001; Ogino and Wilson 2003). A strategy being considered in the United States to target Hispanics who may need higher folate intake is to fortify corn masa flour with folic acid at the same level as enriched cereal grain products. This could prevent an estimated 40 cases of NTDs annually (Tinker et al. 2013).

Antiepileptic Drugs (AEDs)

Hernández-Díaz et al. compared the safety of antiepileptic drugs during pregnancy. Using the North American Pregnancy Registry, the risk of NTDs among infants exposed to specific AEDs during the first trimester of pregnancy were calculated and compared to unexposed controls. Risk was 1.2% for valproic acid, 0.29% for carbamazepine, 0.22% for levetiracetam, and 0.13% for lamotrigine, compared to 0.12% in an external reference population (Hernández-Díaz et al. 2012).

Diabetes Mellitus

Diabetes existing at the earliest stages of pregnancy, during the period of organogenesis, predisposes women to having an infant born with an NTD. Abnormally elevated maternal glucose levels leads to increased glucose transport to the embryo. There is evidence that maternal diabetes significantly reduces expression of *Pax3*, which is associated with NTDs. *Pax3* encodes a transcription factor that inhibits p53-dependent apoptosis. Excess glucose metabolism appears to reduce expression of *Pax3*, resulting in increased p53-dependent apoptosis of neuroepithelium and ultimately greater risk for NTDs (Fine et al. 1999; Loeken 2005).

Obesity

Maternal obesity increases the risk of an NTD. In a meta-analysis, Rasmussen et al. found odds ratios for an NTD-affected pregnancy to be 1.22 for overweight women, 1.70 for obese women, and 3.11 for severely obese women (Rasmussen et al. 2008). The effect of obesity on NTD risk is independent of race, age, education, smoking, alcohol/drug use, diabetes, multivitamin use, and history of an NTD-affected pregnancy (Shaw et al. 1996; McMahon et al. 2013). Interestingly, there is evidence that the NTD-protective effect of folate may be greater in obese women (McMahon et al. 2013).

Prenatal Diagnosis

Improved antenatal testing and screening has necessitated early involvement of pediatric neurosurgeons in the care of women and families with pregnancies complicated by NTDs. Antenatal counseling regarding preparation for the delivery and care for the affected infant can impact the decision of whether families wish to continue with or terminate pregnancies.

Antenatal screening is routinely initiated with testing of maternal serum alpha-fetoprotein (MSAFP) levels and second trimester fetal anatomical ultrasonography. If high, and under appropriate conditions, MSAFP may reliably predict the risk for NTDs. If both MSAFP and ultrasonography are abnormal, amniocentesis may be performed to improve diagnostic accuracy and to assess for possible associated genetic conditions.

Maternal Serum Alpha-Fetoprotein

Alpha-fetoprotein is a glycoprotein that is initially formed by the yolk sac and then sequentially by fetal gastrointestinal tract and liver (Main and Mennuti 1986). Fetal serum AFP levels peak between 10 and 13 weeks' gestation and then gradually decline thereafter. AFP is excreted via the kidneys in fetal urine and therefore is also detectable in amniotic fluid. AFP also appears in lower concentrations of maternal serum and peaks at 28–32 weeks' gestation, which forms the basis for noninvasive screening of NTDs during pregnancy (Main and Mennuti 1986).

The MSAFP levels are measured at multiples of a median value, with unaffected pregnancies of

similar gestational age as controls. When used under appropriate conditions, MSAFP provides an age-specific and patient-specific risk profile of an NTD. The MSAFP may be performed anywhere between 14 and 21 weeks' gestation; however, the optimal time for testing is between 16 and 18 weeks' gestation. Second trimester MSAFP diagnostic accuracy ranges from 70% to 90%, as a number of other conditions may also result in elevated MSAFP (Wilson et al. 2014; Wald et al. 1977). If the risk predicted by MSAFP is greater than 1:500, then subsequent evaluation with repeat MSAFP testing or anatomical ultrasonography is suggested. Incorrect age, multiple pregnancies, unanticipated fetal death, and other fetal abnormalities may all result in abnormal MSAFP values. The lists of other fetal abnormalities resulting in elevated MSAFP are extensive but include gastrointestinal abnormalities such as duodenal atresia, esophageal atresia, omphalocele, and gastroschisis and genitourinary abnormalities including congenital nephrosis, polycystic kidneys, and renal agenesis (Main and Mennuti 1986; Wald et al. 1977). The screening and diagnostic value of MSAFP continues to decrease in the face of rapidly evolving noninvasive fetal imaging techniques (Wilson et al. 2014).

Ultrasonography

Second-generation anatomical ultrasound performed by a skilled ultrasonographer at 18–22 weeks' gestation is the screening modality of choice for NTDs because of its safety, cost efficiency, and detection sensitivity. Detection rates for NTDs up to 94% have been reported using ultrasonography (Boyd et al. 2008). Serial transverse sections of each vertebral segment are required to detect a bifid spine and spinal cord defect. Accuracy of anatomic level of defect within one level for open spina bifida ranges from 64% to 79% using ultrasonography (Kollias et al. 1992), and this must be kept in mind when counseling patients regarding prognosis. In addition to visualizing spinal defects, ultrasonography may be used to confirm approximate gestational age and number of fetuses and also screen for additional congenital anomalies including hydrocephalus and Chiari II malformation, both of which are associated with myelomeningoceles. The "lemon sign" refers to scalloping frontal bones and concavity of the parietal bones on transverse plane. The "banana sign" refers to the abnormal shape of the midbrain and cerebellum in Chiari II malformations. Lemon and banana signs are both seen in 97% of fetuses with spina bifida (Watson et al. 1991). In patients with suspected spina bifida, serial ultrasound imaging can be useful for evaluation of ventricular size and configuration.

Amniocentesis

In patients with abnormal ultrasound findings, and elevated MSAFP, amniotic fluid sampling for karyotyping, AFP, and acetylcholinesterase may be offered. The sensitivity and specificity of amniotic AFP levels have been reported to be up to 100% and 99%, respectively (Crandall and Matsumoto 1984). The positive predictive value of amniotic AFP correlates with high a priori risk for NTD. If done in patients with low a priori risk, the ratio of false positive to true positive using only AFP is 4:1. Therefore, typically, amniotic acetylcholinesterase levels are measured concurrently. Acetylcholinesterase is an isoenzyme that's used as a neurotransmitter in neural tissue. A small proportion of acetylcholinesterase is secreted into amniotic fluid, and none is typically found in maternal serum. With open neural tube defects, communication of the CSF with amniotic fluid results in elevated levels of amniotic acetylcholinesterase. Fetal blood contamination during amniotic fluid sampling can affect both AFP and acetylcholinesterase, although this affects the latter to a lesser degree. Nevertheless, the odds of neural tube defects are significantly greater if both amniotic AFP and acetylcholinesterase are elevated (Collaborative Acetylcholinesterase Study Group 1981).

Amniotic fluid sampling may also be used for fetal karyotyping. The rate of chromosomal abnormalities varies from 2.6% to 25% for spina bifida, and the degree of variability depends on the

presence of additional structural abnormalities. Trisomies 18 and 13 and triploidy are the most common chromosomal abnormalities, and the information gained from fetal karyotyping may influence counseling and decision-making of expecting families (Kennedy et al. 1998; Hume et al. 1996).

MRI

The safety profile of fetal magnetic resonance imaging (MRI) has not been definitively established. What is known is that fetal MRI using 1.5 Tesla magnets may be performed safely in any trimester (Shellock and Crues 2004). In the context of use for NTDs, fetal MRI may be used for confirmation of diagnosis when ultrasound and/or biochemical testing results are equivocal or when ultrasound imaging may be technically challenging to acquire (e.g., maternal obesity, polyhydramnios). These images are usually obtained between 19 and 24 weeks' gestation (Mirsky et al. 2015). Unfortunately, there are no standard imaging references, and thus, a highly specialized interpreter who is knowledgeable regarding the complexities of the developing normal and abnormal fetal brain and spinal cord is required. In addition to aiding in diagnosis, fetal MRI may have the potential to delineate important anatomy that may be pertinent to in utero treatments.

Prenatal Counseling

Given the significant neurological disability associated with NTDs, neurosurgeons may be asked to comment on neurological prognosis as part of antenatal counseling. The objective is to provide unbiased information without imparting one's own beliefs or values.

Anencephaly is uniformly considered a lethal condition, and therefore pregnancy interruption may be offered to women at any gestational age, if desired (Jaquier et al. 2006). Women who wish to proceed with pregnancy in fetuses with this condition must understand that they are exposing themselves to potentially serious pregnancy complications such as antepartum hemorrhage, pre-eclampsia, and gestational diabetes. Most fetuses with anencephaly will die in utero, with a third of neonates surviving greater than 24 h and non-surviving for longer than 10 days (Jaquier et al. 2006).

With continuous improvements in antenatal and neonatal care, the survival and quality of life of patients with open spina bifida have drastically improved in decades past. For spina bifida, four major issues that require addressing are continence, mobility level, cognitive functioning, and associated conditions. The patient's ambulatory status will largely depend on the motor level of deficit, in addition to orthopedic complications, such as club foot. The prenatal anatomic level determined by ultrasound, neonatal motor level, and child motor level are not always correlative. In approximately three-quarters of cases, the prenatal anatomic level will accurately reflect the child's functional motor outcome (Coniglio et al. 1996). Just over 50% of children will be community ambulators, with or without the use of ambulatory assistive devices. Nearly 25% will be non-ambulatory, while the majority of the remainder will be ambulatory at home. Nearly 85% of patients will be socially continent of urine and feces; however, only approximately 5–15% will have normal urinary continence (Steinbok et al. 1992; Swank and Dias 1992). Nearly 60% of children with spina bifida attended regular schooling performing at their grade level. Approximately 80% of patients will require shunt placement for hydrocephalus within the first year of life, and approximately 50% of these patients will require shunt revision within that year (Steinbok et al. 1992; Adzick et al. 2011).

Perinatal Management

Given the complexity of patients with NTDs, a multidisciplinary approach with specialists competent in the management of these patients is necessary. Although neurosurgeons may not directly be involved in the intrapartum care of patients with NTDs, a basic overview and

understanding is necessary for comprehensive care. Fetuses should be delivered at a center with a level III NICU and access to specialized neurosurgical care (Wilson et al. 2014). In patients with spina bifida, lower limb dysfunction and macrocephaly frequently lead itself to breech presentation, and therefore delivery by caesarian section is generally necessary in these cases. In fetuses with vertex presentation, there is some evidence suggesting that vaginal delivery may confer risk of additional loss of neural function from pressure on exposed nerve roots. However, the evidence is not clear, and therefore mode of delivery should be left at the discretion of the treating obstetrician and mother (Wilson et al. 2014; Cochrane et al. 1991; Luthy et al. 1991). Given the increased incidence of latex allergy among this population, latex-free gloves should be used to minimize latex sensitization when handling the neonate (Cremer et al. 1998).

After delivery, like in all births, the primary concerns are cardiorespiratory stability. Once the neonate is deemed stable, the defect should be examined and cleaned with sterile saline. It is important to note and document the defect location, size, and degree of CSF leakage, if any. The defect should then be covered with a sterile saline-soaked dressing, and the trunk may then be wrapped circumferentially with plastic wrapping to prevent dehydration, heat loss, and contamination of the defect (McLone 1998). The infant is then placed in either prone or lateral position in order to avoid pressure on the exposed defect, with the defect elevated above the level of the head to prevent CSF egress. A thorough neurological examination is required to assess the motor level of the neonate and severity of hydrocephalus. This should include assessment of fontanelle and cranial sutures, cranial nerve examination, fundoscopic examination, observation of spontaneous activity, degree of activity in response to noxious stimuli, deep tendon reflexes, and anocutaneous reflex. An assessment for cutaneous signs of possible tandem spina bifida occulta and assessment for kyphoscoliosis are also imperative. Lastly, the neonate should also be evaluated for associated abnormalities including clubbed feet, hip dysplasia, and structural anomalies of the cardiorespiratory system, ribs, gastrointestinal system, and genitourinary system. The vast majority of patients experience significant urologic difficulties including neurogenic bladder, recurrent urinary tract infections, anatomical genitourinary abnormalities, and chronic renal insufficiency. As such, a pediatric urologic specialist should be involved early in the care of these patients. It is important to note that newborns that are unable to spontaneously urinate should undergo clean intermittent catheterizations, and appropriate post-void residuals should be noted for patients (Snow-Lisy et al. 2015).

Typically, a full brain and spinal MRI is obtained in order to delineate the anatomy of the defect and to assess for the presence of a Chiari II malformation and to rule out other associated intracranial pathologies. The patient is closely monitored for symptoms and signs of raised intracranial pressure and Chiari II malformation, including lethargy, weak cry, central apnea, bradycardia, dysphagia, and stridor. Head circumference should be recorded on a daily basis to assess for trends that may require further investigation. Serial cranial ultrasound may also be obtained in the neonatal period to determine trends in ventricular configuration. Abdominopelvic ultrasound may also help identify common associated abnormalities in the genitourinary and gastrointestinal systems. Newborns with open spina bifida typically present with a degree of incomplete spinal cord dysfunction with signs of myelopathy. The anus is usually patulous with flaccid rectal tone (Stark 1971). Blood cultures should be drawn for baseline assessment of bacteremia, and patients should be started on broad spectrum antibiotics with adequate CNS penetration.

Repair of Defect

The primary goal for open spina bifida closure is to isolate of neural tissue and CSF from the external environment in order to reduce the risk of meningitis. Definitive evidence suggesting that early postnatal closure improves the degree of neurologic function does not exist. It is suggested that the defect be closed within 72 h if possible in

order to reduce the risk of meningitis and ventriculitis as delayed closure has a fivefold increased chance of developing infectious complications (McLone 1998; Charney et al. 1985).

From the use of noninvasive fetal monitoring, it was noted that fetuses with NTDs experienced progressive neurological deterioration. For example, fetuses with myelomeningocele experience progressive paraparesis to paraplegia and worsening hindbrain herniation with increasing gestational age (Caldarelli et al. 1996; Korenromp et al. 1986). Preclinical research provided evidence to support the notion that prenatal surgery may preserve neurological function and reduce the incidence of hindbrain herniation. However, any benefits of prenatal surgery should be weighed against maternal and fetal morbidity.

The Management of Myelomeningocele Study (MOMS) is the largest multi-institutional randomized controlled trial to evaluate the safety and efficacy of prenatal surgery for repair of myelomeningocele (Adzick et al. 2011). The trial was conducted from 2003 to 2010 at three maternal-fetal surgery centers in the United States. Subjects enrolled were mothers with singleton pregnancies and fetuses with upper boundary of open defect between T1 and S1, evidence of hindbrain herniation on antenatal imaging, and gestational age of 19–26 weeks, at time of randomization. Subjects were randomized to early fetal surgery or standard postnatal surgery for repair of defect. The trial was terminated prior to completion on the grounds of efficacy for prenatal surgery. At 12 months of age, prenatal surgery reduced the need for shunt placement by one half (40 vs. 82%) and was associated with decreased incidence of hindbrain herniation (64 vs. 96%). Larger ventricular size at time of prenatal surgery was associated with increased need for shunting in those undergoing fetal surgery. When the ventricles measured to be 15 mm or larger using head ultrasound, prenatal surgery did not result in reduced need for ventricular shunting (Tulipan et al. 2015). Moreover, at 30 months of age, there were significant improvements in motor functioning including ambulatory status, and significant improvements in neuropsychomotor development tests. However, the benefits of prenatal surgery detailed above were balanced by significant maternal and fetal complications including increased rates of preterm delivery and intraoperative complications. Given the results of this trial, the American College of Obstetrics and Gynecology suggests that fetal closure of open spina bifida be performed at facilities with expertise in technique, services, and required operative and postoperative multidisciplinary care. It is important that the option of fetal surgery and its unknown long-term effectiveness be outlined to families with fetuses affected by myelomeningocele.

Surgical Technique (Sutton et al. 2012; Gaskill 2004)

During induction of general anesthesia and endotracheal intubation, the infant is kept in the lateral decubitus position or supported supine, so as to avoid pressure on the defect. A latex-free Foley catheter is inserted. The patient is positioned prone on chest and hip bolsters to ensure the abdomen is able to hang freely. Care is taken to ensure all pressure points are padded. A dose of preoperative antibiotic is given. The back is prepped widely with povidone-iodine solution. Sterile drapes are applied, including a 3 M™ Ioban drape.

The operative microscope is brought into the field, or, alternatively, surgical loupes can be used for magnification. A No. 15 blade is used to create an elliptical incision in the skin, just outside the junction of the normal full-thickness skin with the zona epitheliosa (Fig. 2). CSF samples are sent for aerobic and anaerobic culture. The incision is carried through the subcutaneous tissues until dura or fascia is encountered. A plane of dissection is developed, and the base of the sac is mobilized medially using Metzenbaum scissors until it is seen to enter the fascial defect. The placode is then freed by cutting radially into the cuff of dystrophic epidermis/arachnoid and excising it circumferentially around the placode (Fig. 3). Nerve exiting from the placode and terminating in the zone epitheliosa or further laterally can be sacrificed, as they are nonfunctional. Other nerves should be preserved. Diligence is exercised in ensuring all dermal remnants are removed, in

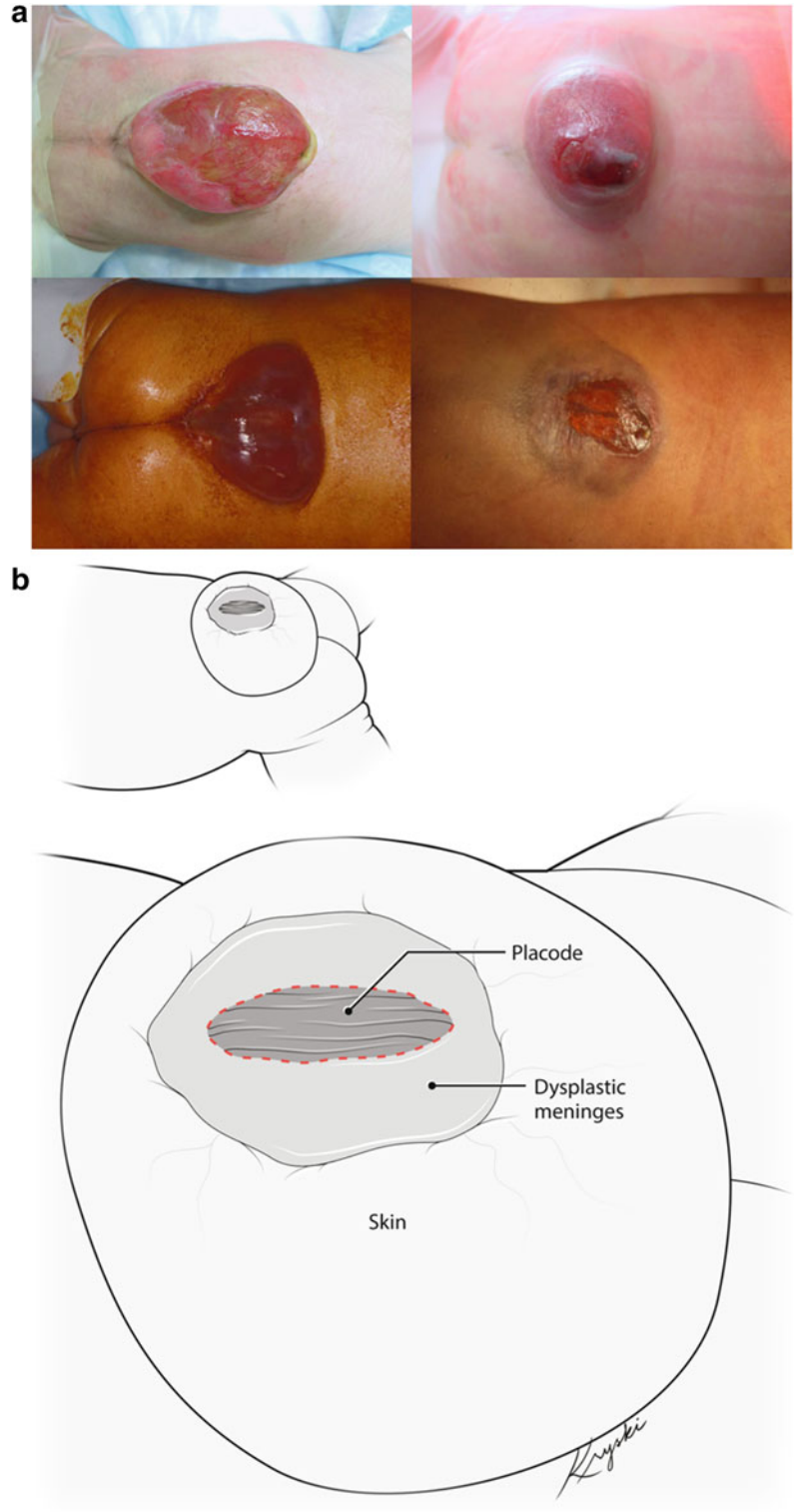

Fig. 2 (**a**) The range of appearances of open neural tube defects of the spine. (**b**) Diagram illustrating the important distinction between the placode and the surrounding dysplastic meninges

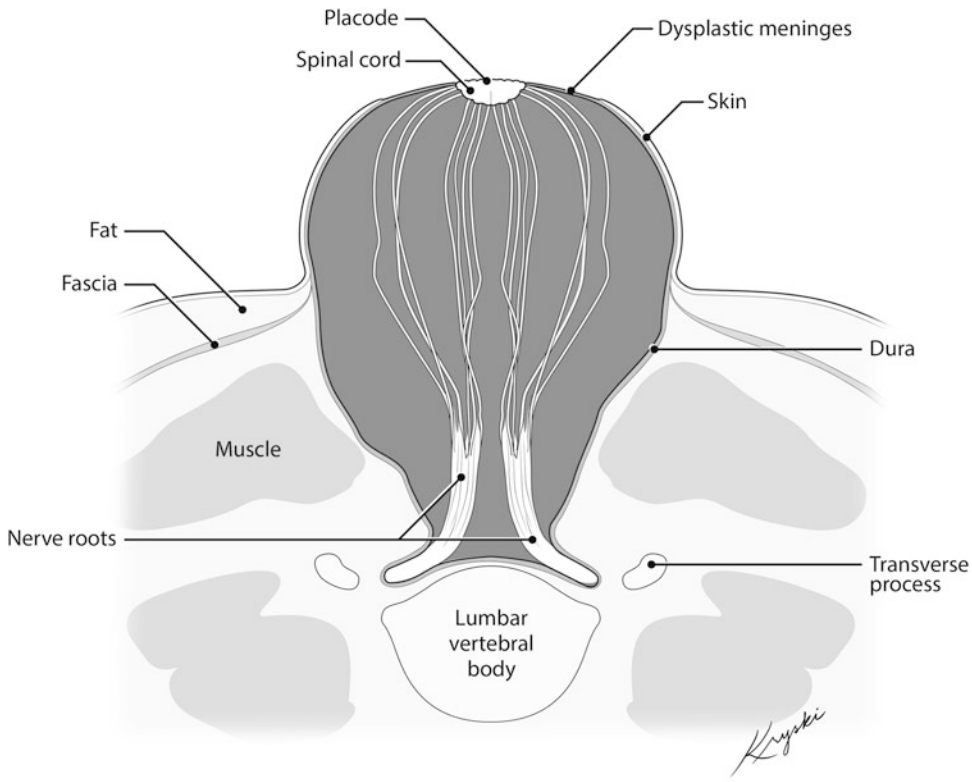

Fig. 3 Axial cross-sectional view of a typical myelomeningocele lesion

order to prevent the possibility of future lipoma or dermoid formation.

The goal of separating the placode is to permit reconstruction of the normal neural tube and prevent future tethering. The placode is reconstructed by placing interrupted 6–0 monofilament non-absorbable sutures to approximate the pia-arachnoid of one side of the placode with the other (Fig. 4). This allows the neural placode to better fit inside the dural canal and allows a pial surface to be in contact with the closed dural to prevent tethering. The everted dura on either side of the defect is undermined using Metzenbaum scissors and reflected medially. The dura is closed in a watertight fashion using a running 5–0 suture. Optionally, the fascia can then be incised in a semicircle fashion on either side, elevated from the underlying muscle, and reflected medially. The fascia is closed with a running 4–0 suture. The skin is undermined and mobilized on either side by using Metzenbaum scissors. The skin is closed using absorbable 5–0 suture. Musculocutaneous and/or cutaneous flaps (e.g., Z-plasties) performed by a specialized plastic surgeon may aid in the closure of large defects.

Postoperative Care

There is a lack of robust evidence guiding the postoperative care of neonates with open spina bifida, and therefore this is generally directed by the preference of the treating surgeon. Patients are generally kept on perioperative antibiotics for 24 h after surgery or until initial blood cultures return as sterile. Neonates should be nursed prone or on their side, with the area of defect closure above the level of the head to minimize CSF leakage. A plastic drape may be placed above the gluteal folds to protect the wound from

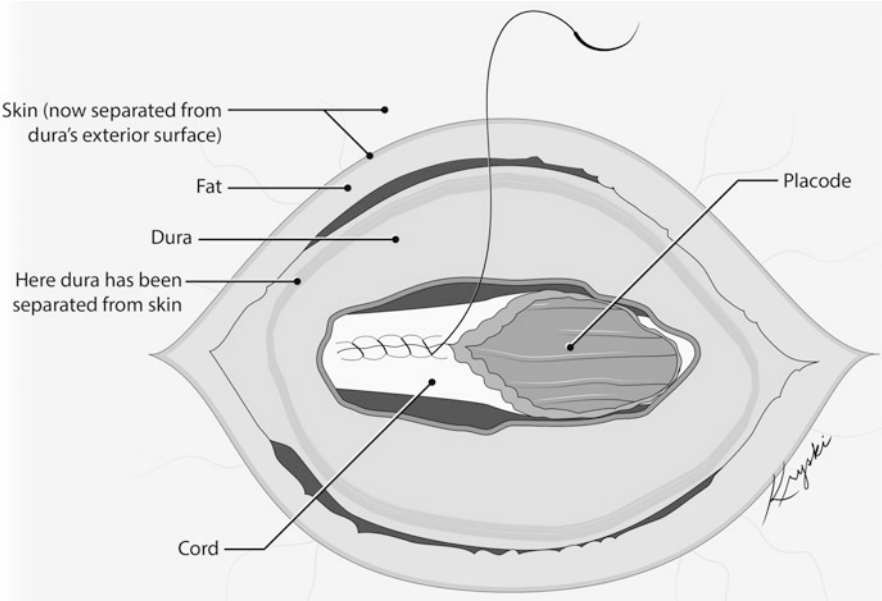

Fig. 4 Reconstitution of the neural tube after release of the placode

soilage. The patient should be monitored closely for brainstem signs, particularly apnea and bradycardia, with daily head circumference measurements. Patients should also continue receiving clean intermittent catheterization regularly in addition to spontaneous voiding.

Superficial wound dehiscence and postoperative wound infection are the most common complications following open spina bifida repair (Pang 1995). Larger wounds have increased risk for CSF leakage. CSF leakage may be a sign of worsening hydrocephalus that may require CSF diversion, either temporarily or permanently. Local wound infections occur in approximately 1–1.5% of cases and are typically treated with frequent wound dressing changes and antibiotics. Neonates are also at high risk for developing neonatal meningitis from local soilage of the defect. Abscesses may also form at the site of repair and may extend toward the thecal sac (Pang 1995). MRI of the lumbar spine should be obtained when abscess is suspected. Broad spectrum antibiotics, with consideration of ventricular tap for narrowing of speciation may be considered. If the CSF is contaminated, any existing shunt system should be externalized. Patients with abscesses extending toward the thecal sac may require repeat operation for source control.

Associated Conditions

Hydrocephalus

The etiology of hydrocephalus in children with open spina bifida, although not yet clearly elucidated, is likely multifactorial. Non-communicating hydrocephalus may be due to fourth ventricular outlet obstruction or secondary to aqueductal stenosis or adhesions. Communicating hydrocephalus may be secondary to underdevelopment of arachnoid granulations or scarring at the level of arachnoid granulations. In patients with open spina bifida, up to 60–80% of children will require CSF diversion within the first year of life (Adzick et al. 2011; Tulipan et al. 2015; Chakraborty et al. 2008). While in hospital, children should have baseline intracranial imaging (head ultrasound, head CT, or brain MRI) to assess ventricular size and configuration and

other associated intracranial abnormalities. Neonates should have active surveillance of head circumference and ventricular size with cranial imaging in the weeks following myelomeningocele repair. Neonates should be clinically monitored for signs of raised intracranial pressure, leakage or bulging of myelomeningocele repair, and also brainstem signs suggestive of Chiari II malformation as these may be exacerbated by raised intracranial pressure. It is also possible that ventricular size may increase without an increase in head circumference or signs of raised intracranial pressures as the immature white matter tracts in the neonate have higher relative compliance. Patients with asymptomatic increase in ventricular size should be monitored closely for need for CSF diversion. If patients are discharged home without CSF diversion, families should be counseled to monitor their newborn closely.

Nearly half of shunted children with spina bifida will require a shunt revision in their first year of life (Caldarelli et al. 1996). Approximately three-quarters of malfunctions are due to mechanical obstruction, while one-quarter are due to infective etiologies. Moreover, more severe ventricular dilatation prior to shunting, and higher levels of spinal defect are associated with increased incidence of shunt malfunction. The order in which myelomeningocele repair and CSF shunting are carried out also influenced the incidence of infective complications. Neonates who are shunted prior to myelomeningocele repair may have the highest rate of shunt infections, followed by children who are shunted simultaneous to myelomeningocele repair, followed by those who are shunted after myelomeningocele repair (Caldarelli et al. 1996).

There is emerging evidence that ETV combined with choroid plexus cauterization (ETV-CPC) may be used as an alternative to traditional CSF diversion strategies in children with hydrocephalus and open spina bifida. The initial experience with ETV-CPC has been described in developing countries, and has yet to be definitively replicated in developed countries (Warf and Campbell 2008).

Chiari II Malformation

Chiari II malformation is present in nearly all patients with open spina bifida and is characterized radiographically by the herniation of the developing cerebellum and brainstem through the foramen magnum, in addition to other radiographic findings. Not all infants experience symptoms secondary to Chiari II malformation; however, symptomatic Chiari II malformation remains the leading cause of death in neonates with spina bifida (McLone 1998; Park et al. 1983). Signs and symptoms of Chiari II malformation include obstructive or central apnea, bradycardia, stridor, dysphagia, dysarthria, aspiration, upper extremity weakness, opisthotonus, hypotonia, and spasticity. Between 10% and 20% of infants with open spina bifida less than 8 months of age will develop brainstem signs suggestive of Chiari II malformation requiring treatment (Pang 1995; Park et al. 1983; Worley et al. 1996).

Patients presenting with brainstem symptoms should receive prompt attention and treatment. For neonates who have not had CSF diversion, a ventricular shunt should be placed. If brainstem signs and symptoms persist postoperatively, then craniocervical junction decompression is warranted. For those who have had a shunt placed, shunt malfunction should be ruled out, and if symptoms persist, then patients should undergo craniocervical decompression. Treatment of hydrocephalus and Chiari II malformation should be performed promptly in order to prevent further progression of symptoms and irreversible damage (Pollack et al. 1996). If neurological symptoms persist after proper CSF diversion and craniocervical decompression, then alternative etiologies for symptoms such as tethered cord and progressive syringomyelia should be considered.

MRI of the brain and craniocervical junction may be helpful in planning for posterior fossa decompression. Patients may have a low-lying torcula with a steep-angled tentorium, and the anatomical detail of the MRI can be used in

order to avoid entering the torcula or occipital sinus. Patients may also have extensive spinal cord syringomyelia seen on MRI associated with their Chiari malformation.

Surgical Technique

The nature of hindbrain decompression requires review of the MRI to determine its extent. The goal of the procedure is to decompress the neural elements by removing the bone overlying the displaced cerebellar vermis and hindbrain and also by performing an expansile duraplasty. Patients are positioned prone with the neck flexed and all pressure points padded. Use of neuromonitoring is optional but, if used, can be done as baseline prior to turning prone. A midline incision is made with dissection carried in the midline avascular raphe until the occiput and posterior elements of the cervical spine are exposed. Unlike Chiari I decompression, Chiari II decompression rarely will require an occipital craniectomy; however, it typically will involve an upper cervical laminectomy (with potentially multilevel laminectomy) and possible removal of some foramen magnum. It is prudent that the surgeon pays special attention to the position of the torcula based on the preoperative MRI and intraoperative confirmation with frameless stereotactic navigation systems. Following boney decompression, there is usually an abnormally thickened atlantooccipital band (i.e., dural band) that may be sectioned. Following this, the dura can then be opened to allow for maximal decompression (Fig. 5). The choroid plexus may be found in its extraventricular dorsal position. The surgeon can follow the extraventricular choroid

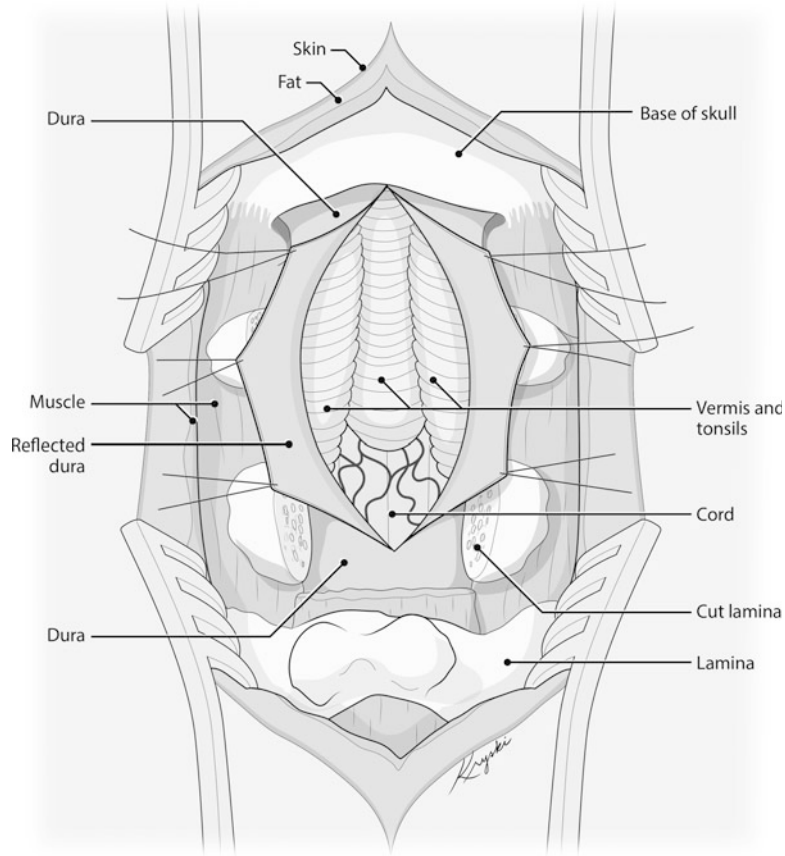

Fig. 5 Diagram illustrating the view after dural opening in a typical Chiari II decompression surgery

plexus, with the option to section any obvious arachnoidal adhesions, to the foramen of Magendie. An expansile duraplasty is performed, and the wound is closed in standard anatomical layers. Some surgeons will not routinely perform a durotomy, given the difficulties and risks inherent in infants. In these cases, intraoperative ultrasonography may be used to confirm that the degree of boney decompression is below the level of the hindbrain herniation. Moreover, some surgeons will also routinely section the arachnoid adhesions tethering the herniated cerebellar tissue to the cervicomedullary junction, if identified.

Orthopedic Abnormalities

Patients with open spina bifida are prone to both congenital and acquired orthopedic abnormalities. These are generally caused by unbalanced muscle action around joints, paralysis, and decreased sensation in the lower extremities. Examples of orthopedic abnormalities include kyphosis, scoliosis, club foot, hip dislocation or subluxation, and ankle and foot abnormalities including rocker bottom deformity, among others (Westcott et al. 1992; Guille et al. 2006). Patients should be followed by a pediatric orthopedic surgeon who may initiate any necessary therapies for the patient in the neonatal period and as the child grows. The goals of orthopedic management are to preserve function and to maximize independence.

Urologic Abnormalities

Nearly all patients with open spina bifida will have problems with storing and releasing urine because the spinal cord lesion affects the voluntary and involuntary control over voiding mechanisms. Patients frequently experience urinary retention and incontinence, which may have significant psychosocial impact. Approximately 30–40% of patients will also have associated renal abnormalities (Müller et al. 2002). A baseline urologic ultrasound allows for the documentation of renal abnormalities and thickness of bladder wall. Urodynamic studies and specialized pediatric urologic follow-up are imperative in the care of infants with open spina bifida. Neonates with difficulties voiding should be started on early trials of clean-intermittent catheterization to reduce the risk of UTI, bladder overdistention, hydronephrosis, and progressive renal failure. Continuous monitoring of urinary habits is important as changes in urination may reflect progressive hydrocephalus or tethered cord (Tarcan et al. 2006).

Latex Allergy

Neonates and children with open spina bifida have a high prevalence of latex sensitivity and allergy. Frequent early hospitalizations with repeated exposure to the latex allergen may play a role in the development of latex allergy (Nieto et al. 1996). In fact, exposure to latex can produce an anaphylactic reaction and is a major health concern. Some patients may be unaware of their sensitivity and may have an anaphylactic reaction at initial exposure (Mazagri 1999). Families and care providers should be counseled on the need for latex precautions in patients with open spina bifida.

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