Improvement in Hindbrain Herniation Demonstrated by Serial Fetal Magnetic Resonance Imaging Following Fetal Surgery for Myelomeningocele

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Myelomeningocele is the most common severe birth defect involving the central nervous system, occurring with an incidence of 4.5 per 10,000 live births. The fetal prevalence is undoubtedly higher, since myelomeningocele is frequently detected by screening amniocentesis and ultrasound, and parents often elect to terminate the pregnancy. In addition to spinal cord dysfunction, children with spina bifida almost invariably have an associated Chiari II hindbrain malformation, consisting of a small posterior fossa and downward displacement of the cerebellar vermis below the foramen magnum into the cervical spinal canal with elongation of the brainstem and obliteration of the fourth ventricle. Approximately 20% of myelodysplastic children develop symptoms of hindbrain, cranial nerve, and spinal cord compression, usually before age 3 months. This is the principal cause of death in this population. In addition, hindbrain herniation with obstruction of the outflow of cerebrospinal fluid (CSF) from the fourth ventricle is believed to be the cause of hydrocephalus, which is present in 85% of individuals with myelomeningocele. In the past, it was believed that the hindbrain herniation that accompanies myelomeningocele was part of an overall cerebrospinal dysgenesis, but there is experimental and clinical evidence that both hindbrain herniation and hydrocephalus are acquired early in fetal life and progress in severity before birth.

See also pp 1819 and 1873.
Fetal surgery for myelomeningocele was first attempted in the human to prevent secondary damage to the exposed spinal cord by amniotic fluid and mechanical trauma. The hypothesis in undertaking correction in utero was that the lower extremity and sphincter function at birth would be better than that expected based on the anatomic level of the dysraphic defect. However, in our initial case, we noted apparent improvement in hindbrain herniation, and, in a series of 4 patients who underwent intrauterine closure, ultrasound images obtained after birth showed a lower than expected incidence of hindbrain herniation. We report our experience with 10 patients who underwent myelomeningocele closure at 22 to 25 weeks of gestation and were observed by means of fetal and postnatal magnetic resonance imaging (MRI) to determine the course of hydrocephalus and hindbrain anomalies.

**METHODS**

**Patient Population**

Beginning in 1997, expectant mothers carrying a fetus diagnosed as having myelomeningocele were offered an extensive evaluation at the Center for Fetal Diagnosis and Treatment at the Children's Hospital of Philadelphia and consideration for fetal surgery. Evaluation consisted of careful review of maternal family and medical history and records of the current pregnancy, including results of fetal ultrasound examinations and amniocentesis. One woman had terminated a previous pregnancy in which the fetus was diagnosed as having severe spina bifida and hydrocephalus, but in all other cases family history was negative for neural tube defects. A psychosocial evaluation was performed, and fetal imaging with ultrasonography and ultrafast MRI assessed leg movement, spinal level of the dysraphic defect, presence of hindbrain herniation, ventricular size, and presence of any associated anomalies. A counseling session with members of the fetal treatment team was then held, and options were discussed. The options available to the woman carrying a fetus with myelomeningocele include (1) termination of the pregnancy prior to 24 weeks' gestation, (2) serial prenatal assessment with planned cesarean delivery near term and immediate postnatal myelomeningocele closure, or (3) fetal surgery.

Between November 1997 and March 1999, 36 women completed the evaluation. Of these, 10 were offered and agreed to fetal surgery, based on predetermined selection criteria. The surgeries were performed between March 1998 and February 1999. The outcome of 1 surgical procedure has been previously reported. The eligibility criteria for fetal closure were estimated gestational age of 22 to 25 weeks at the time of the proposed procedure, atrial diameter less than 17 mm, ultrasound evidence of normal leg and foot motion without clubfoot or other leg deformity regardless of the level of dysraphism, normal karyotype, and no other associated anomalies apart from those typically associated with the myelomeningocele complex. Additional eligibility criteria were no maternal medical risk factors such as obesity, diabetes, or a significant smoking history that could complicate the perinatal course and sufficient family support available to sustain a protracted stay in the Philadelphia area at the Ronald McDonald House.

**Imaging**

After obtaining signed consent from the woman, a fetal MRI was performed using a half-Fourier acquisition single-shot turbo-spin echo sequence on a 1.5-T unit (Siemens Medical Systems Inc, Iselin, NJ). The studies were performed with the woman usually in the supine position and used a body array coil. Sedation was not required. Contiguous slices, 3- to 4-mm each, were obtained of the fetal brain and spine in 3 planes orthogonal to each other. The studies were monitored throughout by a pediatric neuroradiologist to optimize anatomic detail and typically took 30 to 40 minutes to complete.

The initial study was performed at 19 to 23 weeks of gestation. Patients then underwent repeat studies every 3 weeks after surgery during the pregnancy until delivery, and the newborn underwent MRI of the brain and complete spine as soon as he or she was medically stable.

**Surgery**

Prior to surgery, the woman and other family members participated in a group meeting, attended by the fetal team, consisting of the fetal surgeons, neurosurgeon, anesthesiologists, high-risk obstetrician, neonatologist, social worker, and perioperative nursing staff. The results of the evaluation were presented, risks and potential benefits of the proposed surgery were reviewed, and informed consent was obtained. All fetal surgery protocols are reviewed by the institutional Fetal Therapy Advisory Committee.

At the start of surgery, an epidural catheter was inserted, and maternal general anesthesia provided fetal anesthesia and uterine relaxation for open fetal surgery. A low transverse maternal laparotomy and hysterotomy were performed in a location determined by intraoperative ultrasound examination, and the fetal back was exposed. The cystic membrane of the spina bifida lesion was excised from the neural placode and surrounding skin. The first patient underwent a single-layer skin closure with absorbable suture, and a spinal-amniotic shunt was placed. At birth, the spinal drain was not functional, and follow-up of this patient demonstrated symptomatic spinal cord tethering to the skin flap. In the remaining patients, the procedure was modified to a 2-layer closure of acellular human dermis (AlloDerm; LifeCell Corporation, Woodland, Tex) sewn to the fascial defect and followed by primary skin closure. No shunts were placed. In each case, the closure was accomplished in less than one-half hour. Amniotic fluid was replaced with warmed lactated Ringer solution, and the uterine and laparotomy wounds were closed. Postoperatively, tocolysis was maintained with magnesium sulfate intravenous infusion and indomethacin rectal suppositories, followed by

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terbutaline given by a subcutaneous pump. Patients were initially observed in the high-risk obstetric unit, and the pregnant women subsequently kept at bedrest near the hospital for the remainder of gestation. The neonates were delivered by elective cesarean delivery at approximately 36 weeks' gestation after lung maturity was confirmed by amniocentesis, unless premature labor resulted in earlier delivery.

Outcome Measures

The primary end points were gestational age at delivery, birth weight, leg function in the neonatal period, need for shunt placement (head circumference and ventricular size at birth), and severity of the Chiari malformation on each MRI. In order to objectively evaluate the posterior fossa abnormality based on the MRI, a grade was assigned as follows: grade 0, normal; grade 1, visible fourth ventricle and cisterna magna without cerebellar displacement below the foramen magnum, tentorium could be vertically oriented, and tectal beaking could be present; grade 2, visible cisterna magna without displacement of the cerebellum below the tentorium, no visible fourth ventricle; and grade 3, displacement of cerebellum below the foramen magnum and obliteration of all posterior fossa CSF spaces. The grade was assigned by the attending neuroradiologist (L.T.B.). It was not possible to do this in a blinded manner, since the

Table. Data for 10 Patients Undergoing Surgery

<table>
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<th>Patient No.</th>
<th>Gestational Age at First MRI, wk</th>
<th>Spinal Level at First MRI</th>
<th>Ventricle Size at First MRI, mm (Left, Right)</th>
<th>Chiari Grade at First MRI</th>
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<th>Chiari Grade, Postsurgical MRI 3 Weeks</th>
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†MRI indicates magnetic resonance imaging. A ventriculoperitoneal shunt was placed in this patient.

Figure 1. Serial Midsagittal Magnetic Resonance Images (MRIs) From 2 Patients

A, A T2-weighted MRI at 20 weeks of gestation shows vermian/tonsillar herniation (arrowhead) and no fourth ventricle or cisterna magna (patient 8). B, In an MRI of the same patient at 3 weeks after closure, cerebrospinal fluid (CSF) is visible in the fourth ventricle (pointer 1) and cisterna magna (pointer 2). C, An MRI of same patient as a newborn shows that the fourth ventricle (pointer 1) is even more expanded. The tentorium is abnormally vertical, but the posterior fossa has expanded compared with the earlier studies. D, A sagittal T2-weighted MRI obtained in a 22-week fetus with a myelomeningocele prior to surgery (patient 1) shows that the inferior cerebellum is wedge-shaped and impacted into the cervical spinal canal (arrowhead). No CSF is visible in the fourth ventricle or cisterna magna. E, A T1-weighted MRI of the same patient after birth. The cerebellar hernia is now reduced and the fourth ventricle (pointer 1) and cisterna magna (pointer 2) are clearly visible.
approximate age of the fetus and the preoperative or postoperative status was apparent from the MRI studies.

All patients were delivered at the Hospital of the University of Pennsylvania and were initially cared for by the fetal surgery group and neurosurgery group at the Children’s Hospital of Philadelphia. The investigating team made the initial decision regarding shunt placement. Indications for shunt placement were clinical signs of increased intracranial pressure such as macrocephaly, fullness of the anterior fontanelle, or apnea and/or bradycardia. Patients with stable ventriculomegaly without clinical signs did not undergo shunt placement. After discharge from hospital, the patients were referred to a pediatric neurosurgeon and spina bifida group in their community for follow-up care.

RESULTS
There were no maternal deaths or complications in the series and no instances of uterine rupture. Six patients were delivered by elective cesarean delivery at 36 weeks’ gestation after confirmation of fetal lung maturity by amniocentesis. None required respiratory support. Four newborns were delivered earlier than planned (at 25, 30, 30, and 31 weeks’ gestation) because of prematurity labor, and all required initial ventilatory assistance. The 23-week gestation newborn weighed 745 g at birth and died of respiratory insufficiency at age 2 days. The other 3 premature newborns survived. All 9 surviving newborns were discharged to their homes at a mean age of 23 days (range, 4-63 days) and have been followed up for a mean of 182 days (range, 77-473 days).

The myelomeningocele closure was initially well healed in all cases; however, 1 patient (patient 5) required reinsertion at age 1 week because of CSF leakage. At the repeat operation, tethering of the spinal cord to the lateral dural wall, but not to the Alloderm graft, was observed. Another patient (patient 1) required a tethered cord release from the overlying skin (Alloderm was not used) at age 7 months because of loss of leg function below the hips, which was not regained after the procedure. One patient (patient 4) required ventriculoperitoneal shunt placement at age 2 weeks because of frequent apnea episodes in association with mild ventriculomegaly. The anterior fontanelle of this patient was soft, and there were no other signs or symptoms of intracranial hypertension, but the apnea episodes promptly resolved after the procedure. Two patients were offered shunt placement by the treating neurosurgeon in the families’ community based on stable ventriculomegaly without clinical signs of intracranial hypertension or developmental delay, but, after further consideration, shunt placement has not yet been performed in these patients.

The hindbrain abnormality was scored as grade 3 in all of the early fetal (19-24 gestational weeks) preoperative MRIs and reflected hindbrain herniation below the foramen magnum and absence of CSF spaces around the brainstem (FIGURE 1). On the MRI scan done at 3 weeks after fetal closure, all 9 of the surviving fetuses showed improvement; 4 now were rated as grade 2 and 5, as grade 1. By the 6-week MRI, all of the patients were grade 1 (TABLE). The MRI scans performed shortly after birth were also grade 1 (Figure 1). None of these scans showed tonsillar or vermian displacement below the foramen magnum, and all had visible CSF spaces corresponding to the fourth ventricle and cisterna magna, although a vertical tentorium and beaking of the tectum were apparent in all of the patients. At 1 to 13 months of follow-up, none of the infants have manifested clinical signs or symptoms referable to the Chiari II malformation.

Five of 9 evaluable patients had newborn lower extremity function better than expected by at least 2 spinal levels based on anatomic level as determined from the initial fetal MRI. Three patients with thoracic or high lumbar level lesions had function at the L5 level or better (Table). Bowel and bladder continence cannot be evaluated yet because of the young age of the infants.

COMMENT
While fetal surgery has become an accepted treatment for some fatal conditions,14,15 the appropriateness of fetal surgery for nonlethal conditions is controversial.16 Early experiences with fetal ventriculoamniotic shunt placement for severe hydrocephalus were disappointing, and a moratorium was eventually invoked. Recent advances in open fetal surgical techniques and tocolysis have prompted a reexamination of the role of fetal surgery in improving quality of life in certain nonlethal conditions. Although extensive efforts to prevent and detect neural tube defects have resulted in a marked reduction in the number of affected infants, myelomeningocele remains a dev-

<table>
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<th>Gestational Age at Birth, wk</th>
<th>Birth Weight, g</th>
<th>Leg Function at Birth (Left, Right)</th>
<th>Head Circumference at Birth, cm (Percentile)</th>
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astating problem for which postnatal therapy is palliative at best.15 Problems include lower extremity paralysis, shunt-dependent hydrocephalus, bowel and bladder incontinence, and brainstem dysfunction from the Chiari II malformation.

Studies in experimental animals suggest that exposure of fetal neural tissue to the intrauterine environment results in secondary damage to the exposed spinal cord in addition to any dysfunction attributable to the primary spinal cord abnormality.18,19 These experiments involved a surgically created defect, which was not entirely analogous to human myelomeningocele. The models did not produce any of the associated anomalies seen in human myelodysplasia, such as hydrocephalus or the Chiari II malformation. Furthermore, these animal experiments did not resolve the question of when human nervous tissue might be vulnerable during gestation.

A limited amount of human data also provides evidence that at least some of the components of the spina bifida complex are acquired in utero. Autopsy material obtained from human embryos and fetuses with myelomeningocele suggests that neural degeneration occurs at some point during gestation.20,21 In 18 embryos with classic caudal myelodysplasia, Osaka et al7 found an everted neural plate, but most of the membrane coverings were preserved. Interestingly, there was no Chiari II malformation seen in these embryos, whereas the malformation was present in the 2 fetuses with caudal myeloschisis from the same series. Similarly, hydrocephalus was not present in the embryos, but was found in 1 fetus. Babcock et al8 performed serial sonograms on human fetuses with myelomeningocele and found that, whereas only 44% of fetuses aged 24 gestational weeks or younger had ventriculomegaly, 94% of fetuses older than 24 gestational weeks had ventriculomegaly. Furthermore, the degree of hydrocephalus correlated with the amount of posterior fossa deformity.

Early experience with fetal myelomeningocele closure in humans suggested a lower than expected incidence of hindbrain deformity in these infants once they were born. The Chiari II malformation with displacement of cerebellar tissue below the foramen magnum is seen in virtually all newborns with myelodysplasia,12-25 but cerebellar herniation was not present in our first case after early gestation fetal closure9 nor in the 4 cases of late gestation fetal closure reported by Tulipan et al.12 Our previously reported case (patient 1 in the present report) has not required shunt placement at 1 year of follow-up; however, 2 of 4 patients in the series described by Tulipan et al required shunt placement, perhaps because of the late gestation closure.

The major finding in the current series is the rapid reversal of hindbrain herniation and overall increase in the posterior fossa CSF spaces as documented by serial fetal MRI in all 9 surviving fetuses who underwent open myelomeningocele closure at 22 to 25 weeks of gestation. Definite improvement of the Chiari II malformation was evident in all patients on an MRI obtained 3 weeks after the closure. None of the 9 patients had cerebellar herniation present on the newborn MRI, and all patients had a visible fourth ventricle and cisterna magna, which suggests patency of the CSF pathways. Beaking of the midbrain and a vertically oriented tentorium were present in all surviving patients, and so a designation of normal was precluded. However, at present there is no reason to ascribe any adverse consequences to these residual abnormalities. Follow-up in this series of patients has been short, but only 1 of our 9 patients has required shunt placement for clinically overt hydrocephalus, although most of the patients have some degree of ventricular enlargement.

It would be desirable to compare our series with a control cohort of patients who did not undergo fetal closure to eliminate selection bias. Our strict selection criteria for fetal closure arguably preselect a favorable group of patients who might not have required shunt placement even if they had not undergone fetal closure. It is unlikely that a suitable control group can be assembled. Patients who were not considered candidates for fetal closure at our institution would not have been comparable, and the mothers of such patients often either went elsewhere to undergo the fetal procedure or elected to terminate the pregnancy. Women who were offered the procedure invariably chose to proceed with it. Nonetheless, reversal of preexisting hindbrain her-
niation on serial scans coupled with the almost universal presence of the Chiari malformation in the untreated newborn seen historically is compelling.

Reversal of hindbrain herniation after early fetal closure lends support to the unified mechanism of embryogenesis proposed by McLone and Naidich, who suggest that the myelomeningocele allows excessive drainage of ventricular CSF through the open defect and leads to collapse of the rhombencephalic vesicle and a small posterior fossa volume. Growth of the cerebellum and brainstem within a small posterior fossa results in downward herniation and caudal displacement of the cerebellar vermis and brainstem into the cervical spinal canal. Because the outlet of the fourth ventricle is occluded by impacted brain tissue, obstructive hydrocephalus develops either in the fetal period or in the newborn period after closure of the myelomeningocele eliminates the spinal defect as a drainage pathway. By closing the spinal defect early in fetal life, it is likely that back pressure is again established in the posterior fossa, which disimparts the brain from the spinal canal and reestablishes a more normal CSF drainage pathway (Figure 2). Ventricular enlargement, once established, does not appear to resolve, which may be because of the high compliance of the fetal brain. The absence of overt signs of increased intracranial pressure or significant progression of ventriculomegaly seen in these patients suggests a “compensated,” probably communicating, type of hydrocephalus.

Whether longer follow-up will demonstrate a delayed requirement for shunt placement in these patients is unknown. Preventing the problems associated with lifelong shunt dependency as well as those problems associated with brainstem dysfunction attributable to the Chiari malformation itself probably justifies the procedure if the risk can be kept to a minimum and if long-term follow-up confirms that the benefit is maintained. The major risk in all fetal operations is premature labor. The rationale for performing the operation later in fetal life is that if premature labor cannot be controlled, the newborn would have fewer of the well-known complications associated with low birth weight. We have chosen to perform the closure earlier in fetal life, on the grounds that the potential for reversal of secondary injury is more likely to occur. This approach may permit preservation of the regenerative potential of the unmyelinated spinal cord, obviate third trimester damage to the spinal cord, and allow intervention early in the course of progressive ventriculomegaly typical of myelomeningocele fetuses. There was 1 death in our series, directly attributable to lung immaturity in a 745-g newborn, and 3 other patients were delivered prematurely at about 30 weeks’ gestation. None of the surviving patients have suffered intraventricular hemorrhage, major retinopathy, bronchopulmonary dysplasia, or other apparent long-term consequences of prematurity. Risk to the mother appears minimal, since there were no maternal complications.

Five of our surviving patients appeared to have better leg function by at least 2 spinal segments than would have been expected based on fetal imaging studies, although in the first case this was lost by 7 months because of spinal cord tethering to the skin flaps. Although there is very good correlation of prenatally determined anatomic level with ultimate motor outcome in children with spina bifida, short follow-up time, lack of a control group, and a relatively small number of patients prevent drawing any firm conclusions regarding leg function in these infants. However, the data are sufficiently promising to warrant offering fetal closure to selected patients.

REFERENCES