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.1 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 invariable 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.2 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.3,4 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.5 In the past, it was believed that the hindbrain herniation that accompanies myelomeningocele was part of an overall cerebrospinal dysgenesis, but there is experimental6 and clinical7,8 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.

Context Hindbrain herniation occurs in a large percentage of children with myelomeningocele and is the leading cause of death in this population. The effect of early fetal closure of myelomeningocele on hindbrain herniation is unknown.

Objective To determine whether early fetal closure of myelomeningocele affects hindbrain herniation.

Design Case series of patients undergoing fetal myelomeningocele closure with serial measurements of hindbrain herniation and a mean follow-up of 182 days.

Setting Tertiary care medical center.

Participants Ten patients undergoing fetal myelomeningocele closure at 22 to 25 weeks’ gestation between March 1998 and February 1999.

Main Outcome Measures Need for shunt placement; degree of hindbrain herniation (grades 0-3) found on magnetic resonance imaging (MRI) performed prior to surgery and 3 and 6 weeks after fetal surgery, as well as shortly after birth; gestational age at delivery.

Results All initial fetal MRI scans performed at 19 to 24 weeks’ gestation showed significant (grade 3) cerebellar herniation and absence of spinal fluid spaces around the cerebellum. Six fetuses were delivered electively at 36 weeks’ gestation after lung maturity was established. The other 4 were delivered prematurely, at 25, 30, 30, and 31 weeks of gestation, and the 25-week gestation neonate died. All 9 surviving neonates showed improvement in the hindbrain hernia at the 3-week postoperative fetal scan (grade 2, n = 4; grade 1, n = 5). On the postnatal scan, all patients showed grade 1 hindbrain herniation. Only 1 patient required placement of a ventriculoperitoneal shunt.

Conclusion In this series of patients, fetal myelomeningocele closure resulted in improvement in hindbrain herniation as demonstrated by serial MRI scans.

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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 intensive 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, neonurosurgeon, 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...
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>
<thead>
<tr>
<th>Patient No.</th>
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<th>Prenatal, Postoperative Evaluation</th>
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<tr>
<td></td>
<td>Gestational Age at First MRI, wk</td>
<td>Spinal Level at First MRI</td>
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<tr>
<td>-------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
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<td>22</td>
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</tr>
<tr>
<td>2</td>
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<tr>
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*MRI indicates magnetic resonance imaging.
†A ventriculoperitoneal shunt was placed in this patient.
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Evaluate at Birth

<table>
<thead>
<tr>
<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>
<th>Ventricle Size at Birth, mm (Left, Right)</th>
<th>Chiari Grade at Birth</th>
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<tr>
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<tr>
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While fetal surgery has become an accepted treatment for some fetal conditions, the appropriateness of fetal surgery for nonlethal conditions is controversial. Early experiences with fetal ventriculoperitoneal 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-
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astating problem for which postnatal therapy is palliative at best.17 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 myelschisis from the same series. Similarly, hydrocephalus was not present in the embryos, but was found in 1 fetus. Babcook et al5 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,22-25 but cerebellar herniation was not present in our first case after early gestation fetal closure27 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-

Figure 2. Embryogenesis of the Chiari II Malformation

A. The unified theory of embryogenesis of the Chiari II malformation postulates that downward displacement of the cerebellar vermis and tonsils (a) occurs because of negative pressure in the spinal canal generated from drainage of spinal fluid from the open myelomeningocele (b). B. After fetal closure, positive back pressure reduces the cerebellar hernia and expands the posterior fossa.

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tion on serial scans coupled with the almost universal presence of the Chiari malformation in the untreated newborn born historically is compelling.

Reversal of hindbrain herniation after early fetal closure lends support to the unified mechanism of embryogenesis proposed by McLone and Naïdich, 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 disimpaacts 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, obviating the need for third trimester damage to the spinal cord, and allowing 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