OBSTETRICS

Preschool neurodevelopmental outcome of children following fetal myelomeningocele closure

Enrico Danzer, MD; Marsha Gerdes, PhD; Michael W. Bebbington, MD; Deborah M. Zarnow, MD; N. Scott Adzick, MD; Mark P. Johnson, MD

OBJECTIVE: We sought to investigate the preschool neurodevelopmental outcomes of children following fetal myelomeningocele (fMMC) surgery.

STUDY DESIGN: Prior to the Management of Myelomeningocele Study trial, 54 children underwent fMMC closure at our institution. Thirty (56%) returned at 5 years of age for standardized neurocognitive examination. Scores were grouped as high-average, average, mildly delayed, and severely delayed by SD intervals.

RESULTS: Mean verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), and full intelligence quotient (FIQ) scores were within normal population range. High-average or average scores for VIQ, PIQ, FIQ, and processing speed were found in 93%, 90%, 90%, and 60%, respectively. Mean FIQ and processing speed of nonshunted children were significantly higher than for those who required shunt placement ($P = .02$ and $P = .01$, respectively). Mean VIQ and PIQ tended to be higher in nonshunted fMMC children ($P = .05$).

CONCLUSION: The majority of fMMC children in this highly selective population had average preschool neurodevelopmental scores. fMMC children who did not require shunt placement were more likely to have better scores.

Key words: fetal surgery, hindbrain herniation, myelomeningocele, neurodevelopmental outcome, spina bifida, ventriculomegaly

Cite this article as: Danzer E, Gerdes M, Bebbington MW, et al. Preschool neurodevelopmental outcome of children following fetal myelomeningocele closure. Am J Obstet Gynecol 2010;202:x.ex-x.ex.

Myelomeningocele (MMC) is a devastating congenital malformation with complex physical and neurodevelopmental sequelae that affects approximately 1 in every 2000 live births. MMC is characterized by defective fusion of the caudal neural tube and exposure of the meninges and neural tissue to the intrauterine environment. Depending on the level of neural tube defect, MMC results in variable degrees of lower extremity motor and sensory deficits, fecal and urinary incontinence, and sexual dysfunction. In addition to the spinal cord dysfunction, significant problems in MMC arise from hydrocephalus and hindbrain herniation as part of the Chiari II malformation. The incidence of hydrocephalus associated with MMC ranges between 70-90% and the children are usually shunt dependent for life.[1-4] Hydrocephalus adversely affects intellectual outcome and results in late morbidity and mortality caused by shunt malfunction or infection. Generally, children with MMC are at increased risk for neurocognitive impairments, poor school achievement, social challenges, language deficits, and visual motor integration (VMI).[5]

Prior to 1997, fetal surgical intervention was considered only for fetuses with life-threatening anomalies.[6,7] However, the severe morbidity and significant mortality associated with MMC combined with compelling experimental evidence in animal models that demonstrates the neurological deficits in MMC are acquired early in fetal life and progress in severity throughout gestation led to consideration of prenatal intervention for MMC.[8] Early clinical experience in human beings suggests that ongoing damage to the spinal cord might be alleviated by in utero closure and that fetal intervention potentially improves hindbrain herniation, ventriculoperitoneal shunt rate, and neurofunctional outcome.[4,9-13]

We recently reported on short-term neurodevelopmental outcomes of children who underwent fetal MMC (fMMC) surgery at our institution.[14] We found that at 2 years of age approximately two thirds of fMMC children had cognitive language and personal social skills in the low-average to average range. Despite these promising initial results it is currently unknown whether fMMC closure impacts on long-term cognitive and developmental outcomes given the fact that neurodevelopmental skills during early childhood (<3 years) may not be necessarily predictive of outcome in later life.[14] It is possible that the neurodevelopmental deficits identified in our previous study were transient or, conversely, greater deficits may emerge over time. We have continued to follow up this population of children who underwent fMMC surgery prior to the National Institutes of Health (NIH)-sponsored Management of MMC Study (MOMS) trial to investigate preschool

From the Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, Philadelphia, PA.

Received Sept. 23, 2009; revised Jan. 25, 2010; accepted Feb. 2, 2010.

Reprints: Mark P. Johnson, MD, Center for Fetal Diagnosis and Treatment, Children's Hospital of Philadelphia, Fifth Wood Center, 34 St. and Civic Center Blvd., Philadelphia, PA 19104. johnsonma@e.mail.chop.edu.

0002-9378/$36.00

doi: 10.1016/j.ajog.2010.02.014

TABLE 1
Selection criteria for fetal myelomeningocele repair at Children's Hospital of Philadelphia

- <26 wks' gestation
- Confirmed normal karyotype
- Absence of associated congenital malformations
- Maximum lateral ventricular diameter of <17 mm
- Severe Arnold-Chiari II malformation
- ≥S1-level lesion
- Normal leg movement and absence of talipes deformity

Danzer. Neurodevelopmental outcome of children following fMMC closure. Am J Obstet Gynecol 2010.

neurodevelopmental and cognitive performance.

Materials and Methods

Patient population

This study was approved by the Committee for Protection of Human Subjects Institutional Review Board (IRB# 2000-11-2081). From January 1998 through February 2003, 58 patients met our inclusion criteria (Table 1) and underwent fMMC closure. All infants were subsequently delivered by cesarean section and received neonatal care at our institution. Details of the preoperative evaluation, surgical approach, and postnatal management have been described previously.[8,11,13,14] Data collected from maternal prenatal charts, postnatal hospital charts, and follow-up records included gestational age at fetal intervention, anatomical lesion level, and clinical outcomes. Operative reports of shunt placement, if performed, were reviewed to determine timing and indications for shunt placement. Neurosurgical criteria for ventriculoperitoneal shunt placement have been previously described.[12] Families were asked to return for follow-up at 1, 2, 3, and 5 years of adjusted age. Each visit included evaluations by a pediatrician, physical therapist, developmental psychologist, radiologist, neurosurgeon, and urologist. Neurodevelopmental testing was administered by either a trained psychologist or psychometrist, supervised by a pediatric psychologist (M.G.). The neurodevelopmental outcome data from their follow-up visit form the basis of this study.

Neurodevelopmental assessment at 1, 2, and 3 years of age

The protocol for the neurodevelopmental assessment has been described elsewhere.[14] Briefly, development was assessed by the Bayley Scales of Infant Development (BSID), 2nd edition, and the Preschool Language Scales-III (PLS) for cognitive development. The BSID is a well-standardized assessment measure for children from birth-3 years of age that generates 2 separate scores. The Mental Developmental Index (MDI) evaluates cognition, language, memory, problem solving, and social skills, and the Psychomotor Developmental Index assesses fine and gross motor skills. The PLS is a standardized assessment of speech and language, and consists of PLS-EXP (expressive) that evaluates use of expressive language and PLS-REC (receptive) that assesses comprehension of language. Both the BSID and PLS yield scores that are normalized to a mean of 100 ± 15. Therefore, a score of ≤70 is >2SD below the mean. Scores were grouped as average, mildly delayed, and severely delayed by SD intervals (115-85, 71-84, <70).

Neurodevelopmental assessment at 5 years of age

Cognitive testing

The Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III), was administered to assess cognitive function.[15] The WPPSI-III is a widely used, standardized assessment tool shown to be both valid and reliable. The scales are comprised of 10 verbal and performance subtests and yield verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), full intelligence quotient (FIQ), and processing speed (PS) scores (expected mean: 100 ± 15). Scores were grouped as above average, average, mildly delayed, and severely delayed by SD intervals (≥116, 115-85, 71-84, <70). The Vineland adaptive behavior scale was administered to assess cognitive function in those children whose delays prevented completion of WPPSI-III testing.

Achievement testing

fMMC children were evaluated with the Woodcock-Johnson Psychoeducational Battery-Revised[16] that evaluates academic performance in reading (letter identification and passage comprehension) and math (calculation and applied problems) that are scaled with a mean 100 ± 15.

Tests of VMI

The Beery-Buktenica Developmental Test of VMI was used to assess visual spatial and VMI ability (mean, 100 ± 15).[17] The test involves copying of geometric forms and is designed to identify potential learning problems.

Test of Differential Abilities Scales

The test of Differential Abilities Scales (DAS) is a standardized intelligence test for assessing general verbal and nonverbal functioning.[18] Scores are reported in form of a t score. The average t score is 50 ± 10.

Statistical analysis

Descriptive statistics, 2-sided *t* test, and median test were used for statistical comparison to evaluate the overall clinical and early neurocognitive outcome between fMMC survivors who returned for serial follow-up evaluation and those who did not return.

To evaluate the neurodevelopmental outcome, fMMC children who returned for follow-up were divided into 2 groups: nonshunted vs shunted. The 2-sided *t* test, median test, and logistic regression analysis were used for statistical comparisons as appropriate. $P < .05$ was considered statistically significant. All statistical tests were performed using a statistical software package (JMP, version 7.0; SAS Corp, Cary, NC).

Results

Patient population

Prior to the National Institute of Child Health and Human Development-MOMS trial, 58 patients underwent fMMC closure at our institution. All fMMC children were delivered ≤36-37 weeks of gestation because of preterm rupture of membranes, preterm labor, or the obstetrical risks associated with the maternal hysterotomy and their overall

TABLE 2
Fetal myelomeningocele patient demographics

Demographic	All fMMC children (n = 54)	fMMC children evaluated at 5 y (n = 30)	fMMC children who did not return (n = 24)	*P* value
GA at fetal surgery (wk, mean ± SD)	23.1 ± 1.4	23.0 ± 1.1	23.3 ± 1.6	.46
GA at delivery (wk, mean ± SD)	34.7 ± 2.5	35.4 ± 1.8	33.9 ± 2.9	.03
Birthweight (g, mean ± SD)	2482.6 ± 586.5	2689.7 ± 479.3	2223.9 ± 614.2	< .001
Median Apgar score at 1 min (range)	8 (1-9)	8 (1-9)	8 (2-9)	.91
Median Apgar score at 5 min (range)	9 (6-10)	9 (6-10)	9 (7-9)	.28
Maximum prenatal VM (mean ± SD)	11.1 ± 2.4	11.2 ± 2.5	11.1 ± 2.2	.58
Maximum postnatal VM (mean ± SD)	16.1 ± 4.2	16.5 ± 4.1	15.8 ± 4.3	.23
Increase in lateral ventricular width (mean ± SD)	4.9 ± 2.9	5.3 ± 3.1	4.9 ± 2.6	.19
VP shunt placement for symptomatic VM	26 (48%)	14 (47%)	12 (50%)	.46
Age at shunt placement (mo, mean ± SD)	5.4 ± 2.9	4.9 ± 2.8	6.1 ± 3.1	.32
Median level of lesion (range)	L4 (T8-S1)	L4 (T12-S1)	L4 (T8-S1)	.45
Ambulatory status at age 5 y[9]				.66
Independent	37 (69%)	22 (73%)	15 (62%)	
Assisted walking	13 (24%)	6 (20%)	7 (30%)	
Wheelchair dependent	4 (7%)	2 (7%)	2 (8%)	

fMMC, fetal myelomeningocele; *GA*, gestational age; *VM*, ventriculomegaly; *VP*, ventriculoperitoneal.

Danzer. Neurodevelopmental outcome of children following fMMC closure. Am J Obstet Gynecol 2010.

clinical outcome has been extensively described elsewhere.[12] Four pregnancies were lost due to complications of severe prematurity following delivery for uncontrolled preterm labor at 25, 26, 27, and 27 weeks of gestation, respectively. Overall neonatal survival following fMMC surgery was 93%.

Forty-nine of the 54 (91%) survivors returned at least once for detailed neurodevelopmental assessment during the first 5 years of life. Overall, 37 (68%) returned for follow-up evaluation at 1 year, 30 (56%) at 2 years, 29 (54%) at 3 years, and 30 (56%) at 5 years. Baseline characteristics and fetal surgery details of fMMC children who returned and those who did not return for detailed assessment at 5 years of age are summarized in Table 2. There were no differences in time of fetal surgical intervention, MMC lesion level, degree of ventriculomegaly progression, incidence of ventriculoperitoneal shunt placement, and overall ambulatory status between groups. However, mean birthweight and mean gestational age at delivery were statistically significantly lower in fMMC children who did not return compared to those who did return.

Neurodevelopmental assessment <3 years of age

To evaluate whether children who returned serially and those who did not had different early neurodevelopmental outcomes, comparisons were made among the mean MDI, Psychomotor Developmental Index, PLS-EXP, and PLS-REC scores at the latest available evaluation of children who only returned for their 1-, 2-, or 3-year assessment and the 1-, 2-, or 3-year scores of fMMC children who underwent preschool neurodevelopmental assessment at 5 years of age. As demonstrated in Table 3, mean neurodevelopmental scores were similar between groups, suggesting that early neurodevelopmental outcomes of fMMC children who returned for the 5-year evaluation were similar to those who did not return.

The early (<36 months of age) neurological outcomes grouped by SD intervals for fMMC children who returned for the preschool assessment at 5 years of age (average, mildly delayed, and severely delayed range) are summarized in Table 4. As previously reported,[14] children who did not require shunt placement for symptomatic ventriculomegaly scored significantly more often within the average range than shunted fMMC during the neurocognitive assessment during the first 3 years of age.

Neurodevelopmental assessment at 5 years of age

In the cohort of 30 patients who returned for the 5-year neurodevelopmental assessment, there were 14 female and 16 male fMMC children. Shunt rate was 47% (14/30). Mean age at assessment was 61 months (median, 61; range, 54–71). Operative variables and baseline demographics were similar between nonshunted and shunted fMMC children who underwent preschool evaluation (data not shown).

For the entire cohort mean WPPSI-III VIQ, WPPSI-III PIQ, WPPSI-III FIQ, and WPPSI-III PS was 100.8 ± 18.9 (median, 101; range, 50–131), 93.1 ± 15.1 (median, 96; range, 50–114), 95.4 ± 16 (median, 98; range, 50–124), and 93.9 ± 16.8 (median, 85; range, 50–128), re-

TABLE 3
Infant comparative neurodevelopmental outcomes

Variable	fMMC children evaluated at 5 y	fMMC children who did not return	*P* value
12 mo MDI	87.0 ± 15.5 (92; 50–107)	90.1 ± 13.2 (90; 58–107)	.52
12 mo PDI	56.7 ± 9.2 (54; 50–88)	56.1 ± 6.2 (57; 50–67)	.81
12 mo PLS-EXP	87.4 ± 14.3 (84; 50–113)	90.2 ± 14.3 (85; 71–113)	.58
12 mo PLS-REC	84.5 ± 12.9 (85; 50–119)	94.5 ± 14.1 (89; 79–121)	.05
24 mo MDI	91.5 ± 18.6 (96; 50–112)	94.6 ± 13.0 (94; 72–118)	.60
24 mo PDI	58.1 ± 11.5 (52; 50–88)	57.6 ± 12.5 (50; 50–87)	.92
24 mo PLS-EXP	87.5 ± 19.7 (97; 50–117)	93.6 ± 10.0 (94; 77–108)	.78
24 mo PLS-REC	92.8 ± 21.0 (92; 50–135)	90.5 ± 13.0 (89; 71–113)	.26
36 mo MDI	92.7 ± 16.2 (97; 50–114)	86.1 ± 18.1 (95; 54–103)	.41
36 mo PDI	66.0 ± 14.9 (66; 50–97)	61.9 ± 12.5 (63; 50–82)	.47
36 mo PLS-EXP	94.7 ± 17.7 (97; 50–133)	97.0 ± 9.8 (98; 84–111)	.68
36 mo PLS-REC	100.6 ± 20.3 (102; 50–137)	97.0 ± 14.1 (103; 81–112)	.65

fMMC, fetal myelomeningocele; *MDI*, Mental Developmental Index; *PDI*, Psychomotor Developmental Index; *PLS-EXP*, Preschool Language Scales-III–expressive language; *PLS-REC*, Preschool Language Scales-III–receptive language.
Data presented as mean ± SD (median; range).

Danzer. Neurodevelopmental outcome of children following fMMC closure. Am J Obstet Gynecol 2010.

spectively. Thus mean WPPSI-III VIQ, mean WPPSI-III PIQ, mean WPPSI-III FIQ, and mean WPPSI-III PS for the entire fMMC cohort was similar to population norms. High-average or average scores for WPPSI-III VIQ, WPPSI-III PIQ, WPPSI-III FIQ, and WPPSI-III PS were found in 93%, 90%, 90%, and 60% of all fMMC children. Mean FIQ and PS scores of nonshunted children were significantly higher than those for children who required shunt placement ($P = .02$ and $P = .01$, respectively). Mean VIQ and PIQ of nonshunted children tended to be higher than the mean VIQ and PIQ in the shunted group, although this did not reach statistical significance ($P = .05$ and $P = .07$, respectively) (Table 5). The neurocognitive outcomes, stratified by SD intervals for nonshunted and shunted fMMC children, are shown in Figure 1.

The results of the Woodcock-Johnson Psychoeducational Battery achievement tests demonstrate mean scores for the group that was similar to expected population mean score (Table 6). Risk for learning disability, defined as an achievement score 15 points lower than the mean score, and significant learning disabilities, defined as an achievement score 2SD below the mean score, were noted in 4 (13%, 3 with shunt) and 3 (10%, all with shunt) fMMC children, respectively.

The mean VMI score for the entire fMMC cohort was 88.3 ± 19.0 (median, 90; range, 50–120), which is in the low-average range compared to population norms. fMMC children who required shunt placement for progressive ventriculomegaly tended to have lower VMI scores than nonshunted fMMC patients, but no statistical difference was found between groups (nonshunted: 94.1 ± 18.3 [median, 96; range, 57–120] vs shunted: 81.8 ± 18.3 [median, 83; range, 50–103], $P = .07$). Also when grouped according to SD intervals, 69% of the nonshunted fMMC children had normal VMI scores, 25% demonstrated mild to moderate delays, and 6% presented with

TABLE 4
Stratified infant neurocognitive outcomes

	Entire study cohort			Nonshunted			Shunted		
Variable	Average	Mildly delayed	Severely delayed	Average	Mildly delayed	Severely delayed	Average	Mildly delayed	Severely delayed
12 mo MDI	65%	22%	13%	79%[a]	21%	0%	44.4%	22.2%	33.3%
12 mo PLS-EXP	45.5%	45.5%	9%	62%[a]	38%	0%	22.2%	55.6%	22.2%
12 mo PLS-REC	64%	31%	5%	85%[a]	15%	0%	33%	56%	11%
24 mo MDI	70%	15%	15%	80%[a]	20%	0%	50%	12.5%	37.5%
24 mo PLS-EXP	60%	15%	25%	84%[a]	8%	8%	25%	25%	50%
24 mo PLS-REC	65%	25%	10%	92%[a]	8%	0%	25%	50%	25%
36 mo MDI	82%	9%	9%	91%[a]	9%	0%	73%	9%	18%
36 mo PLS-EXP	70%	25%	5%	82%[a]	18%	0%	56%	33%	11%
36 mo PLS-REC	80%	15%	5%	91%[a]	9%	0%	67%	22%	11%

MDI, Mental Developmental Index; *PLS-EXP*, Preschool Language Scales-III–expressive language; *PLS-REC*, Preschool Language Scales-III–receptive language.
Data presented as percent.

[a] $P < .01$ (average nonshunted vs average shunted fetal myelomeningocele children).

Danzer. Neurodevelopmental outcome of children following fMMC closure. Am J Obstet Gynecol 2010.

TABLE 5
WPPSI-III preschool neurocognitive outcomes

Variable	Entire study cohort	Nonshunted	Shunted	*P* value
WPPSI-III VIQ	100.8 ± 18.9 (101; 50–130)	107 ± 12.9 (102; 86–130)	93.6 ± 22.3 (95; 50–131)	.05
WPPSI-III PIQ	93.1 ± 15.1 (96; 50–114)	97.6 ± 7.1 (97; 88–114)	87.9 ± 19.9 (92; 50–112)	.07
WPPSI-III FIQ	95.4 ± 16.0 (98; 50–124)	101.4 ± 7.3 (99; 92–121)	88.6 ± 20.4 (89; 50–124)	.02
WPPSI-III PS	87.3 ± 16.8 (85; 50–128)	93.9 ± 10.7 (94; 78–119)	79.3 ± 20 (80; 50–128)	.01

FIQ, full intelligence quotient; *PIQ*, performance intelligence quotient; *PS*, processing speed; *VIQ*, verbal intelligence quotient; *WPPSI-III*, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.
Data presented as mean ± SD (median; range).
Danzer. Neurodevelopmental outcome of children following fMMC closure. Am J Obstet Gynecol 2010.

significant delays; while in the shunted fMMC group the VMI scores were normal, mildly to moderately delayed, and severely delayed in 50%, 14%, and 36%, respectively.

Memory abilities were assessed using the DAS assessment. Although the mean t score for the DAS assessment of recall of objects (40.6 ± 11.2 [median, 43; range, 20–61]) remained within the average SD interval, 50% of nonshunted fMMC children and 45% of shunted fMMC children had recall of objects scores below average. The mean T-score for the DAS assessment recognition of pictures of the fMMC cohort (46.3 ± 6.6 [median, 46; range, 28–58]) was slightly lower than the population norms. Interestingly, compared to the recall of objects scores, none of the nonshunted children and only 20% of the shunted children had recognition of pictures scores that were below average.

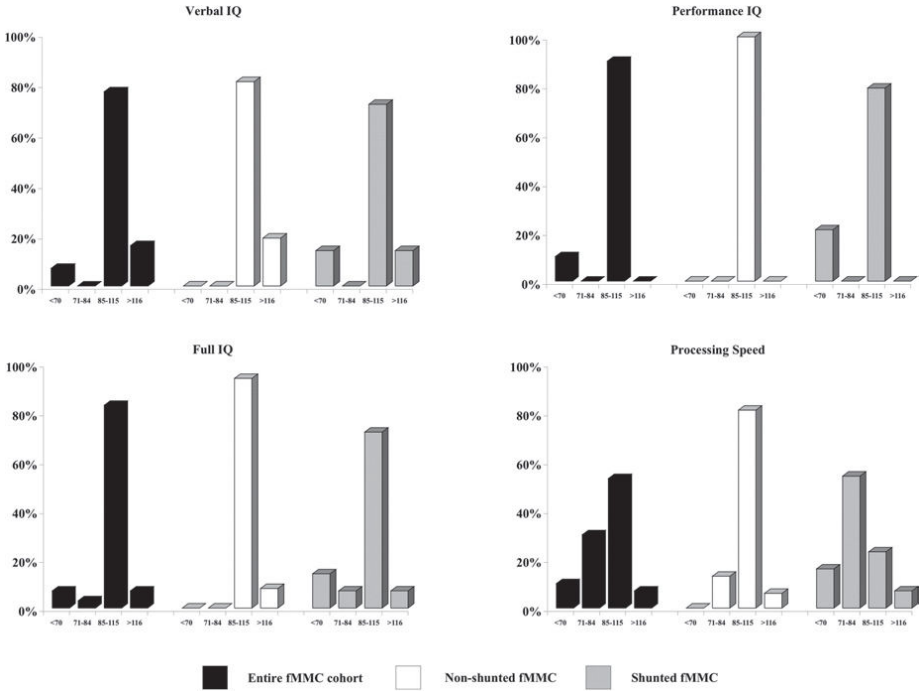
Serial assessment of neurodevelopmental outcome

When early MDI scores where compared to the 5-year VIQ scores we found an improvement in neurocognitive status in 60% of fMMC children who returned for serial follow-up assessment (Figure 2). Of those, 50% improved their overall neurodevelopmental status from mildly delayed at 2 years of age to average scores at 5 years or from an average to a high-average score. The remaining 50% improved their scores, but remained within SD intervals. The observed upward trend appeared to be independent of shunt status as 60% of the nonshunted and 58% of the shunted fMMC children improved their neurocognitive scores.

Comment

It is increasingly recognized that assessment of neurodevelopmental outcome is fundamental in the evaluation of the impact of novel medical and surgical interventions. Preliminary data suggest that midgestational MMC closure reverses hindbrain herniation and subsequently favorably impacts on brain stem function, reduces the requirement for ventriculoperitoneal shunt placement, and enhance short-term lower extremity and ambulatory status.[4,9-14] However, long-term neurocognitive outcomes following fMMC surgery have not yet been reported. We therefore evaluated the impact of prenatal intervention on neurodevelopmental outcome during preschool age in a cohort of surviving children who underwent maternal-fetal

FIGURE 1
WPPSI-III preschool neurocognitive outcomes



Plot of test scores for Wechsler Preschool and Primary Scale of Intelligence, Third Edition, verbal intelligence quotient (IQ), performance IQ, full IQ, and processing speed for fetal myelomeningocele (fMMC) children undergoing standardized cognitive testing. Percentage of patients is shown on y-axis, and tests scores are displayed on x-axis. Expected population mean score is 100 with SD of 15.
WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third edition.
Danzer. Neurodevelopmental outcome of children following fMMC closure. Am J Obstet Gynecol 2010.

TABLE 6
Preschool psychoeducational achievement testing

Variable	Entire study cohort	Nonshunted	Shunted	*P* value
WJ read	106.7 ± 21.3 (109; 50–142)	112.8 ± 10.3 (114; 95–130)	99.2 ± 28.7 (105; 50–142)	.09
WJ L-W	105.6 ± 20.5 (110; 50–136)	111.3 ± 8.0 (111; 95–126)	98.7 ± 28.3 (100; 50–136)	.1
WJ attack	113.4 ± 14.4 (111; 83–139)	115.1 ± 10.5 (111; 97–135)	111.4 ± 18.7 (106; 83–139)	.5
WJ math	101.9 ± 16.9 (107; 45–129)	103.6 ± 11.1 (107; 84–112)	99.3 ± 23.3 (101; 45–129)	.5
WJ applied	103.2 ± 17.4 (103; 45–129)	106.8 ± 11.4 (105; 86–125)	98.5 ± 22.8 (100; 45–129	.2
WJ quant	101.6 ± 12.9 (105; 74–131)	102.9 ± 12.9 (106; 82–121)	99.8 ± 19.2 (100; 74–131)	.6

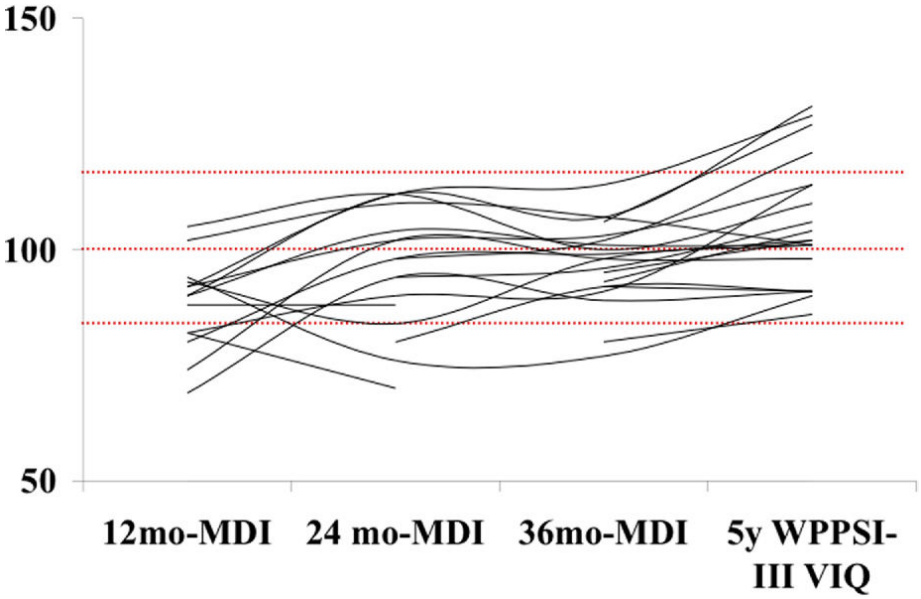
applied, applied problems; *attack*, word attack; *L-W*, letter-word identification; *math*, mathematics reasoning; *quant*, quantitative concepts; *read*, basic reading skills; *WJ*, Woodcock-Johnson. Data presented as mean ± SD (median; range).

Danzer. Neurodevelopmental outcome of children following fMMC closure. Am J Obstet Gynecol 2010.

surgery for MMC prior to the NIH-sponsored MOMS trial. Using clearly defined standardized measurements by examiners who were trained to reliability, we found that the majority of fMMC children have average to high-average preschool neurodevelopmental and cognitive scores. In addition, we observed that fMMC children scored within the average to high-average range for writing, math reasoning, and reading comprehension–academic achievements known to be commonly impaired in MMC children who underwent standard neurosurgical procedures postnatally.[5,19-22] These findings are intriguing, given the fact that results of neurodevelopmental assessments at the age of school entry generally are relatively stable and predictive of long-term outcome and function into adulthood.

Adverse neurocognitive outcome is a recognized complication in children with MMC.[2,5,21,23] Impairment has been related to the synergistic effects of patient-related factors (eg, level of the lesion, number of shunt revision and infections, environmental factors) and the configurational dysmorphologic changes of the developing brain, including hindbrain herniation, dysgenesis of the corpus callosum, malformation of the midbrain and limbic tract, volume loss in the cerebellum and posterior cortex, gray matter heterotopia, and white matter injury.[24-29] An obvious source of neurodevelopmental difficulties is the degree of developmental abnormalities and morbidity associated with severe ventriculomegaly. In agreement with this hypothesis, previous studies demonstrated that postnatally repaired MMC children with shunted hydrocephalus have worse neurodevelopmental and cognitive testing scores than their nonshunted counterparts with asymptomatic ventriculomegaly.[2,21,30,31] We also found that fMMC children who required ventriculoperitoneal shunt placement had lower neurodevelopmental and cognitive scores than nonshunted fMMC children. However, it is important to note that in contrast to postnatally repaired MMC cohorts that required shunt placement, shunted fMMC children had mean VIQ, PIQ, and FIQ scores that remained within the average to low-average range. In our fMMC cohorts overall shunt rate was 48%, which is lower than the reported 70-90% described in postnatally repaired MMC population.[1-4] We previously demonstrated that fMMC closure and subsequent reversal of hindbrain herniation improves overall supra- and infratento-

FIGURE 2
Infant to preschool comparative trends



Evaluation of individual neurodevelopmental scores (*black lines*) of fetal myelomeningocele children who returned serially until 5 years of age. *Dotted lines* represent expected average score ranges for population norms (100 ± 15).

MDI, Mental Developmental Index; *VIQ*, verbal intelligence quotient; *WPPSI-III*, Wechsler Preschool and Primary Scale of Intelligence, Third Edition.

Danzer. Neurodevelopmental outcome of children following fMMC closure. Am J Obstet Gynecol 2010.

rial brain biometry and normalizes extra-axial cerebrospinal fluid hydrodynamics.[10,11] Although intrinsic brain dysembryogenesis undoubtedly exists in MMC, we postulate that the reduced shunt requirement and the better than expected preschool neurocognitive outcome in fMMC children might be explained, at least in part, by the fact that reversal of hindbrain herniation, reestablishment of normal cerebrospinal fluid hydrodynamics, and cessation of progressive ventriculomegaly following fMMC closure may have reduced the development of secondary acquired injury (ie, ischemia, compression) to the vulnerable immature brain during gestation. Our hypothesis is supported by elegant histomorphological studies in embryos, fetuses, and newborns with MMC that revealed the aforementioned dysmorphological changes of the developing brain were absent in early gestation MMC embryos, but present later in gestation and increased in severity with advancing gestational age until birth.[25,32-34]

An important finding in this study is the comparison of early childhood to preschool neurocognitive results. We found an upward trend of neurodevelopmental scores from 2-5 years of age in 60% of fMMC children who had serial measurements available. Of those, 50% improved their overall neurodevelopmental status across SD intervals, while the remaining 50% improved their scores, but remained within SD intervals. Of note, this upward trend was independent of shunt status. Neurocognitive scores of $\leq$70 reflect severe neurocognitive deficits and were found in 2 fMMC children (4% of total fMMC population) and scores did not increase in these fMMC children. Although the incidence of mental retardation following fMMC closure is less than the previously reported 10-15% in postnatally repaired MMC cohorts,[2] these 2 fMMC children with severe neurological deficits deserve further comments on their outcomes. In contrast to the remaining fMMC children the postnatal course of these 2 children (both shunted) was complicated by multiple cyanotic apnea episodes in combination with electroencephalogram-confirmed seizures during the first year of life in one and the development of severe intracranial hemorrhage at the time of shunt revision at 18 months in the other. We believe that these complications likely contributed significantly to the adverse neurocognitive outcome in these patients, based on the more favorable findings in fMMC children without such complications.

Another important aspect of neurocognitive function is visual motor skills. In contrast to the reported significant delays in visual motor coordination in postnatally repaired MMC cohorts,[35,36] we found that visual spatial perception scores for fMMC children as a group were mostly within 1SD of the normative mean VMI scores. However, our results suggest a link between the requirement of shunt placement following fetal intervention and poor visual motor coordination. While nonshunted fMMC children demonstrated only mild deficits in visual recognition and fine motor perception (median VMI score: 96), shunted fMMC children had poorer visual motor coordination skills (median VMI score: 81). The reason for the difference in visual spatial coordination skills in nonshunted vs shunted fMMC children is unknown. We can only speculate whether children who require shunt placement have more extensive underlying dysgenesis or disorganization of their brain regions such as the corpus callosum that allow a more frequent manifestation of dysfunctional visual recognition and fine motor integration than their nonshunted peers. Additional studies are needed to better understand the determinants of poor VMI in fMMC children. Nevertheless, early recognition is important to help prevent learning problems, especially in shunted fMMC children through early intervention, special education, and rehabilitative services.

Although our study provides a number of very intriguing observations, we recognize there are several potential limitations. First, our strict selection criteria for fetal surgery (eg, ventriculomegaly of $<$17 mm, absence of additional non-Chiari II malformation–related brain malformation) may have preselected a more favorable group of patients than in previous reports on neurodevelopmental outcome in postnatally repaired MMC children. In addition environmental factors, such as parent education and socioeconomic status known to be strongly correlated with neurologic and developmental outcomes in other congenital malformations (ie, congenital heart disease),[37,38] may have also influenced overall neurocognitive outcome in our population. Of note, $>$95% of our fMMC parents have college degrees, all mothers are either employed or homemakers, and all fathers are employed. Furthermore, an intact family support system was a requirement before offering fMMC surgery. We appreciate that the higher than expected educational level and socioeconomic status of fMMC families may have been confounding factors in our analysis. Thus our results may not be generalizable to other MMC populations.

Second, although only 56% of the fMMC patients returned for developmental testing at 5 years of age and the potential for a selection bias exists, we have been in yearly contact via telephone interview with all fMMC families to gather follow-up information. Parental report by telephone using a structured interview indicated mainstream schooling with some expectations for additional support for those fMMC children who did not return for assessment (unpublished data, E. Danzer, 2009). Third, we do not have 5-year neurodevelopmental outcome data on postnatally repaired MMC children managed at our center during the same time period for direct comparison and have used previously reported case series for comparison purposes. We acknowledge that consideration must be taken when comparing results from previous studies as discrepant results may partly be due to different management methodology, varying ages at follow-up evaluations, study design, definitions of neurodevelopmental impairment, and different approaches to reporting of cognitive outcome. Fourth, although our study currently provides the longest follow-up for fMMC children it is crucial to remember that our data still represent in-

fant outcomes in a selected population and academic deficiencies and the need for extra educational assistance and social-emotional challenges may not appear until later. Therefore, follow-up evaluations need to be extended through early adulthood to evaluate stability of outcomes. Fifth, the 4 fMMC children (7%) lost because of complications of preterm delivery in our original cohort may deserve comments on the safety, risks, and benefits of fMMC closure. Although perinatal loss is rare in postnatally repaired MMC neonates, 15-30% of MMC children who undergo standard neurosurgical repair die within the first 5 years of life, and the majority of these deaths are attributable to complications associated with severe hindbrain herniation.[39-41] To date there have been no postnatal losses of our original cohort of 54 surviving fMMC children and all had reversal of hindbrain herniation. Furthermore we previously demonstrated that hindbrain herniation–associated brain stem dysfunction is largely absent in our population.[42] Finally, our ability to evaluate potential confounding factors that are associated with adverse neurocognitive outcome following fMMC surgery is limited by the modest sample size of our cohort. Nonetheless, our study provides an important contribution to our developing understanding of the impact of fetal intervention on MMC. Perhaps most importantly, the results of the present study combined with our previous reports provide further support for the rationale for the ongoing NIH-sponsored MOMS trial and underscore the necessity of its completion to allow direct comparison between fetal and postnatal repaired groups for this promising but not-yet-proven treatment alternative for children with MMC.

In summary, we found that surviving children who underwent maternal-fetal surgery for MMC may have better than expected neurodevelopmental and neurocognitive outcome during preschool age compared to previously published series of postnatally repaired MMC children. The majority of fMMC survivors are at an age-appropriate point in schooling. However, our results also demonstrate that fMMC children continue to demonstrate some mild neurocognitive deficits that are characteristic of children with MMC (eg, consistently higher scores in neurocognitive areas than VMI). Thus, continuation of neuropsychological assessment and close monitoring of academic and social adjustment will be important to identify fMMC children who may require appropriate supportive services. ■

REFERENCES

1. Battibugli S, Gryfakis N, Dias L, et al. Functional gait comparison between children with myelomeningocele: shunt versus no shunt. Dev Med Child Neurol 2007;49:764-9.

2. Beeker TW, Scheers MM, Faber JA, Tulleken CA. Prediction of independence and intelligence at birth in meningomyelocele. Childs Nerv Syst 2006;22:33-7.

3. Rintoul NE, Sutton LN, Hubbard AM, et al. A new look at myelomeningoceles: functional level, vertebral level, shunting, and the implications for fetal intervention. Pediatrics 2002; 109:409-13.

4. Tulipan N, Sutton LN, Bruner JP, Cohen BM, Johnson M, Adzick NS. The effect of intrauterine myelomeningocele repair on the incidence of shunt-dependent hydrocephalus. Pediatr Neurosurg 2003;38:27-33.

5. Dennis M, Landry SH, Barnes M, Fletcher JM. A model of neurocognitive function in spina bifida over the life span. J Int Neuropsychol Soc 2006;12:285-96.

6. Adzick NS, Harrison MR. Fetal surgical therapy. Lancet 1994;343:897-902.

7. Danzer E, Sydorak RM, Harrison MR, Albanese CT. Minimal access fetal surgery. Eur J Obstet Gynecol Reprod Biol 2003;108:3-13.

8. Danzer E, Flake AW. In utero repair of myelomeningocele: rationale, initial clinical experience and a randomized controlled prospective clinical trial. Neuroembryol Aging 2007;4:165-74.

9. Danzer E, Gerdes M, Bebbington MW, et al. Lower extremity neuromotor function and short-term ambulatory potential following in utero myelomeningocele surgery. Fetal Diagn Ther 2009;25:47-53.

10. Danzer E, Johnson MP, Bebbington M, et al. Fetal head biometry assessed by fetal magnetic resonance imaging following in utero myelomeningocele repair. Fetal Diagn Ther 2007;22:1-6.

11. Danzer E, Johnson MP, Wilson RD, et al. Fetal head biometry following in-utero repair of myelomeningocele. Ultrasound Obstet Gynecol 2004;24:606-11.

12. Johnson MP, Sutton LN, Rintoul N, et al. Fetal myelomeningocele repair: short-term clinical outcomes. Am J Obstet Gynecol 2003;189: 482-7.

13. Sutton LN, Adzick NS, Bilaniuk LT, Johnson MP, Crombleholme TM, Flake AW. Improvement in hindbrain herniation demonstrated by serial fetal magnetic resonance imaging following fetal surgery for myelomeningocele. JAMA 1999;282:1826-31.

14. Johnson MP, Gerdes M, Rintoul N, et al. Maternal-fetal surgery for myelomeningocele: neurodevelopmental outcomes at 2 years of age. Am J Obstet Gynecol 2006;194:1145-52.

15. Wechsler D. Wechsler Intelligence Scale for Children, 3rd ed. Orlando, FL: The Psychological Corp, Harcourt Brace and Company; 1991.

16. Woodcock RW, Johnson MB. Woodcock-Johnson Test of Achievement-Revised. Allen, TX: DLM Teaching Resources; 1990.

17. Beery KE, Buktenica NA, Beery NA. Developmental Test of Visual Motor Integration. Lebanon, IN: Modern Curriculum Press; 1989.

18. Elliot CD. Differential Ability Scales. San Antonio, TX: Psychological Corp; 1983.

19. Barnes MA, Wilkinson M, Khemani E, Boudesquie A, Dennis M, Fletcher JM. Arithmetic processing in children with spina bifida: calculation accuracy, strategy use, and fact retrieval fluency. J Learn Disabil 2006;39:174-87.

20. Fletcher JM, Barnes M, Dennis M. Language development in children with spina bifida. Semin Pediatr Neurol 2002;9:201-8.

21. Soare PL, Raimondi AJ. Intellectual and perceptual-motor characteristics of treated myelomeningocele children. Am J Dis Child 1977; 131:199-204.

22. Wills KE, Holmbeck GN, Dillon K, McLone DG. Intelligence and achievement in children with myelomeningocele. J Pediatr Psychol 1990;15:161-76.

23. Friedrich WN, Lovejoy MC, Shaffer J, Shurtleff DB, Beilke RL. Cognitive abilities and achievement status of children with myelomeningocele: a contemporary sample. J Pediatr Psychol 1991;16:423-8.

24. de Wit OA, den Dunnen WF, Sollie KM, et al. Pathogenesis of cerebral malformations in human fetuses with meningomyelocele. Cerebrospinal Fluid Res 2008;5:4.

25. Emery JL, Gadsdon DR. A quantitative study of the cell population of the cerebellum in children with myelomeningocele. Dev Med Child Neurol Suppl 1975;35:20-5.

26. Fletcher JM, McCauley SR, Brandt ME, et al. Regional brain tissue composition in children with hydrocephalus: relationships with cognitive development. Arch Neurol 1996;53:549-57.

27. Friede RL. A quantitative study of myelination in hydrocephalus (factors controlling glial proliferation in myelination). J Neuropathol Exp Neurol 1962;21:645-8.

28. Hasan KM, Sankar A, Halphen C, et al. Quantitative diffusion tensor imaging and intellectual outcomes in spina bifida: laboratory investigation. J Neurosurg Pediatr 2008;2:75-82.

29. Vachha B, Adams RC, Rollins NK. Limbic tract anomalies in pediatric myelomeningocele and Chiari II malformation: anatomic cor-

relations with memory and learning–initial investigation. Radiology 2006;240:194-202.
30. Fletcher JM, Copeland K, Frederick JA, et al. Spinal lesion level in spina bifida: a source of neural and cognitive heterogeneity. J Neurosurg 2005;102:268-79.
31. Mirzai H, Ersahin Y, Mutluer S, Kayahan A. Outcome of patients with meningomyelocele: the Ege University experience. Childs Nerv Syst 1998;14:120-3.
32. Gilbert JN, Jones KL, Rorke LB, Chernoff GF, James HE. Central nervous system anomalies associated with meningomyelocele, hydrocephalus, and the Arnold-Chiari malformation: reappraisal of theories regarding the pathogenesis of posterior neural tube closure defects. Neurosurgery 1986;18:559-64.
33. Osaka K, Matsumoto S, Tanimura T. Myeloschisis in early human embryos. Childs Brain 1978;4:347-59.
34. Osaka K, Tanimura T, Hirayama A, Matsumoto S. Myelomeningocele before birth. J Neurosurg 1978;49:711-24.
35. Dennis M, Edelstein K, Hetherington R, et al. Neurobiology of perceptual and motor timing in children with spina bifida in relation to cerebellar volume. Brain 2004;127:1292-301.
36. McLone DG, Czyzewski D, Raimondi AJ, Sommers RC. Central nervous system infections as a limiting factor in the intelligence of children with myelomeningocele. Pediatrics 1982;70:338-42.
37. Forbess JM, Visconti KJ, Hancock-Friesen C, Howe RC, Bellinger DC, Jonas RA. Neurodevelopmental outcome after congenital heart surgery: results from an institutional registry. Circulation 2002;106:I95-102.
38. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G. Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. Pediatrics 2008;121:e759-67.
39. Charney EB, Rorke LB, Sutton LN, Schut L. Management of Chiari II complications in infants with myelomeningocele. J Pediatr 1987;111:364-71.
40. Hoffman HJ, Neill J, Crone KR, Hendrick EB, Humphreys RP. Hydrosyringomyelia and its management in childhood. Neurosurgery 1987;21:347-51.
41. Worley G, Schuster JM, Oakes WJ. Survival at 5 years of a cohort of newborn infants with myelomeningocele. Dev Med Child Neurol 1996;38:816-22.
42. Danzer E, Finkel RS, Rintoul NE, et al. Reversal of hindbrain herniation after maternal-fetal surgery for myelomeningocele subsequently impacts on brain stem function. Neuropediatrics 2008;39:359-62.